An investigation into infertility in Otago and Southland; the prevalence, service use and understanding amongst women

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ABSTRACT

Introduction: Infertility is an important global public health issue. For individuals it can result in grief, depression and deteriorating relationships, and, for societies, generate a costly burden and possibly impact on population growth. Findings from high-income countries, although variable, have suggested approximately a fifth of women had experienced *infertility* (defined as ever trying unsuccessfully to conceive for at least 12 months), with around half of these seeking medical help, and up to a third receiving treatment. Despite the common occurrence of infertility, surveys generally have reported poor knowledge. While New Zealand demographic data highlight delayed childbearing and high proportions of childless women over 40 years, potentially indicating substantial infertility, there has been only limited information about infertility here. This thesis aims to extend current knowledge by estimating the prevalence of infertility, assessing service use and outcomes for infertile women in southern New Zealand, and evaluating fertility knowledge and behaviours.

Methods: To meet this overall aim three studies were conducted: A population-based survey of women living in southern New Zealand aged 25–50 years to determine the proportion having: a) experienced infertility; b) sought help; and c) resolved their infertility, and to assess their fertility knowledge; an analysis of Otago Fertility Service patient data to determine the prevalence and predictors service outcomes; and national hospital discharge data on infertility, and also pelvic inflammatory disease and ectopic pregnancies (both causes of tubal factor infertility), were explored to determine their feasibility for monitoring infertility and the potential generalisability of the southern data nationally.

Results: The survey had 1,125 participants, representing a response rate of 60.1%. Overall, 21.7% (95% CI 19.1–24.4%) had tried unsuccessfully to conceive for at least 12 months, increasing to 25.3% (95% CI 22.6–28.1%) when the definition included women who sought medical help to conceive. The majority (70.6%) of infertile women sought medical help, and 37.9% reported receiving treatment.

Amongst fertility clinic patients, receiving treatment was associated with low parity, younger age, not smoking and having a healthy body mass index. Three-quarters of survey participants and half of the clinic patients resolved their infertility with a live birth. Resolution was associated with a younger age at onset of infertility, being in a heterosexual relationship, being less deprived, having less severe diagnoses and receiving treatment. Knowledge amongst survey participants was particularly poor regarding identifying women's fertile period, although a third reported engaging in ovulation monitoring. Interpretation of national data on hospitalisations for infertility, pelvic inflammatory disease and ectopic pregnancies was substantially hindered by the unknown, but likely substantial, proportion of cases not managed as publicly funded inpatients. Overall this analysis showed that it is not currently feasible to monitor infertility in New Zealand using hospitalisation data.

Discussion: Most findings were consistent with the literature identified from other high-income countries, although survey results suggest infertility could be more common than previously estimated. These data provide insights into infertility in New Zealand and highlight the need for national data on infertility care and outcomes, primary prevention strategies, and improved fertility education.

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Antoinette Righarts.

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ABBREVIATIONS

AI	Artificial insemination
AIC	Akaike information criterion
ART	Assisted reproductive technology
BMI	Body mass index
CATI	Computer assisted telephone interview
CI	Confidence interval
CPAC	Clinical priority access criteria
DHB	District health board
DI	Donor insemination
GP	General practitioner
HR	Hazard ratio
ICD	International Classification of Diseases
ICSI	Intra cytoplasmic sperm injection
IRR	Incidence rate ratio
IUI	Intra uterine insemination
IVF	*In vitro* fertilisation
NHI	Nation health index
NZDep06	New Zealand deprivation score based on the 2006 census
OECD	Organisation for Economic Co-operation and Development
OFS	Otago Fertility Service
OI	Ovulation induction
OR	Odds ratio
PID	Pelvic inflammatory disease
pys	Person years of observation
RR	Risk ratio (synonymous with relative risk)
SES	Socio-economic status
SHR	Sub-hazard ratio
SRS	Simple random sample
STI	Sexually transmitted infection
TFR	Total fertility rate
UK	United Kingdom
USA	United States of America

CHAPTER ONE:

INTRODUCTION

Chapter One provides an introduction to infertility, its importance and trends nationally and internationally. It provides a context to examine information gaps and presents the overall structure of this thesis.

1.1 The burden of infertility

An international review of infertility shows this to be a major problem (Boivin *et al.*, 2007). Based on a commonly used infertility definition of *trying unsuccessfully to conceive for 12 months or more or seeking medical care to get pregnant*, this review concluded that just under 10% of women/couples were currently experiencing infertility, equivalent to 72 million couples worldwide. Around half of affected couples had sought medical care and just under a quarter received a medical intervention. This level of *current* infertility is lower than estimates of the *life-time* experience of infertility, which include the much-used figure of one in every six women experiencing infertility (Gurunath *et al.*, 2011). In fact, previously in 2002, the World Health Organization estimated almost 200 million women in low-income countries alone have experienced infertility (Rutstein and Shah, 2004).

1.2 What is infertility?

Variations in the estimates of the burden of infertility arise, in part, due to the different definitions of infertility. According to the Oxford Dictionary (2014), to be infertile is for a person to be 'unable to reproduce itself; unable to have young'. In demography and other non-medical literature, infertility is concomitant with not having children. However, in medical and epidemiological usage, infertility generally refers only to the inability or reduced ability to conceive a pregnancy. In these latter disciplines, *fecund* refers to the ability, and *infecund* the inability to have a live born child. As infertility may not be absolute, a person may suffer from infertility (i.e. have difficulties conceiving a pregnancy), but still be fecund (i.e. can have a pregnancy ending in a live birth, despite having difficulties conceiving).

Conversely, an individual may be infecund but not infertile (i.e. are able to conceive, but not able to produce a live birth).

1.2.1 Clinical and epidemiological definitions of infertility

Clinical definitions of infertility have been derived to advise on the appropriate timing of infertility investigations for women/couples who have been trying unsuccessfully to conceive, and subsequently used in epidemiological studies (Gnoth *et al.*, 2005).

The cumulative conception rates presented by Taylor (2003) demonstrate that 75% of women conceive after six months of regular unprotected intercourse, and 90% after 12 months. Of the remaining 10%, a reasonable proportion of women will still spontaneously conceive after 12 months, therefore, 12 months or more trying to conceive was historically considered to define *sub-fertility.* Conceptions are more sporadic after 24 months of trying to conceive, therefore, this was considered the time period that defined *infertility*. Taylor (2003) did not specify the characteristics or age range of the women to whom these average conception rates applied, however, a strong association with reduced rates and increasing age was noted (refer to Section 1.4.2 on page 7 for details on the effect of age on female fertility).

Historically this 24-month duration was used to define infertility, however, as infertility investigations are now recommended after a period of 12 months, this shorter period is now used as an operational definition (van der Steeg *et al.*, 2005, American Society for Reproductive Medicine, 2012). Nevertheless, assessment before 12 months may be appropriate if there is a history of any cause for infertility or the woman is aged 35 years or older (Brosens *et al.*, 2004, Gnoth *et al.*, 2005).

It is also valuable to classify infertility into primary and secondary infertility. *Primary infertility* refers to infertility when no previous pregnancy had occurred, and *secondary infertility* when a woman has previously been pregnant. One common measure derived from primary infertility and fecundity status is *primary*

unresolved infertility, meaning primary infertility that has not resolved through at least one conception. This leads to another common fecundity measure reported in infertility literature: *Involuntary childlessness*. Women who are involuntarily childless are infecund; by definition this includes women with primary unresolved infertility, but it may also include women who conceived without difficulties but did not have a live birth and women who did not have the opportunity to conceive. Women, of course, may also be infecund by choice (*voluntary childlessness*).

Whether to use a definition based on time spent *trying* or of *unprotected intercourse* has been debated (Greil and McQuillan, 2010), and may depend on the context. While married women not using contraception in low-income countries have been assumed to be trying to conceive (Mohsen *et al.*, 2001, Liu *et al.*, 2005, Vahidi *et al.*, 2009), this has not always been observed to be the case (Koetsawang *et al.*, 1985). Therefore, in most clinical studies, and in many of population-based studies, infertility is defined by the time spent trying to conceive, rather than the time spent having regular unprotected intercourse without specifically taking into account intention.

Table 1.1 lists the common infertility and infecundity terms, alongside a brief description of the term and other related terms.

Table 1.1: A summary of common infertility and infecundity terms

Terms	Description and common related terms
Infertility, sub-fertility	Did not conceive a pregnancy within a specified time limit (usually, 12 or 24 months), irrespective of whether a pregnancy occurs subsequently. This may be defined as either time spent trying to conceive or having regular unprotected intercourse. *12 (or 24) months trying to conceive*: A common definition, especially in middle and high-income countries, for infertility that is based on time spent trying to conceive. *12 (or 24) months regular unprotected intercourse*: An infertility definition that is more commonly used in low-income countries, based on time spent exposed to the risk of conception (independent of intent).
Resolved infertility	Had a pregnancy* after meeting a definition of infertility.
Unresolved infertility	Has not had a pregnancy* after meeting a definition of infertility.

Table 1.1 ***continued***

Terms	Description and common related terms
Primary infertility	Infertility when no previous pregnancy has occurred.
Unresolved primary infertility	Infertile and never pregnant*, usually measured near to or after the completion of a woman's reproductive life.
Secondary infertility	Infertility after at least one pregnancy has previously occurred.
Currently infertile	Currently meets the definition of infertility in use. *Current prevalence*: The proportion of the population who are currently infertile.
Infecund	Has not achieved a live birth (may or may not have been pregnant, so not necessarily infertile).
Involuntary childlessness	Never had a desired live birth, usually measured near to or after the completion of a woman's reproductive life.
Voluntary childlessness	Never had a live birth and did not want one, usually measured near to or after the completion of a woman's reproductive life.

* *Resolution of infertility is sometimes based on a live birth (rather than just a pregnancy) subsequent to infertility.*

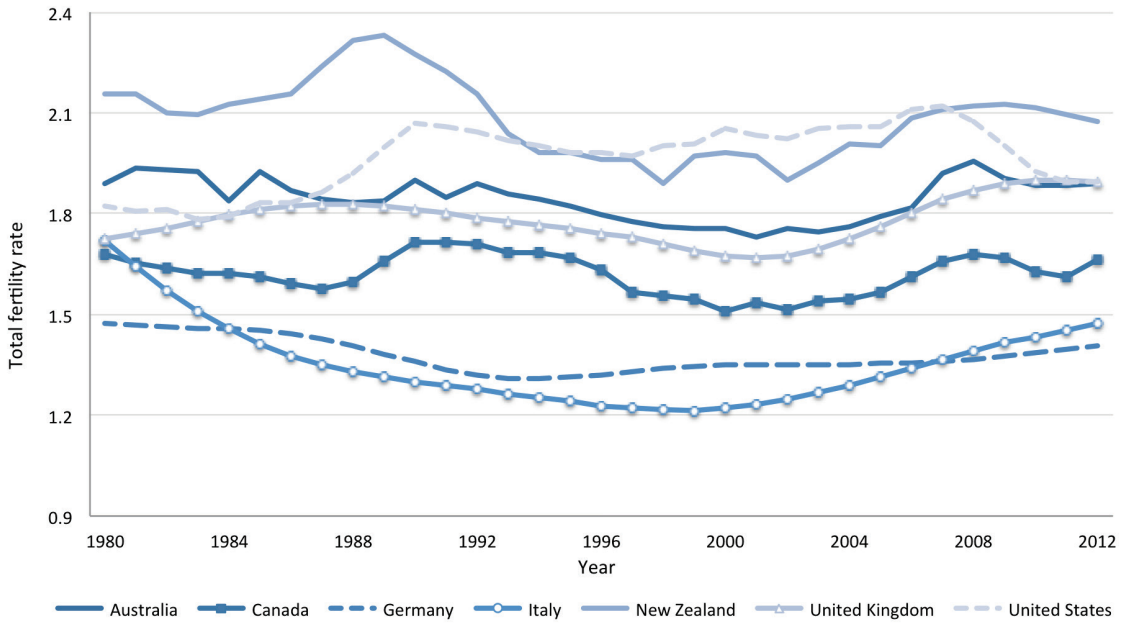
1.3 The Impact of infertility

Infertility may have profound psychological effects on individuals and influence relationships. For individuals, infertility and its treatment is associated with clinically significant symptoms of depression, anxiety, grief and even suicidal tendencies (Domar *et al.*, 1993, Beutel *et al.*, 1999, World Health Organization, 2009). Another important effect of infertility is the disruption to an individual's anticipated life plans (Cousineau and Domar, 2007). For women, the evidence suggests that infertility may significantly reduce their quality of life and result in increased sexual dysfunction and poor relationships (Monga *et al.*, 2004, Chachamovich *et al.*, 2010, Marci *et al.*, 2012). The recent recognition of these consequences has highlighted the need for adequate support services for women and couples with fertility difficulties (Read *et al.*, 2014). It has been suggested that the increasing medicalisation of infertility, especially in middle and high-income countries, has inadvertently led to the emotional responses that individuals and couples may experience being neglected.

The consequences of infertility for individuals may stem from societal expectations; in many cultures, the inability to conceive bears a stigma, with resulting perceived or genuine rejection worsening the anxiety and disappointment that affected women feel (Schmidt *et al.*, 2005). In one study 61% of couples having difficulty conceiving concealed their infertility from family and/or friends, with almost half not disclosing their infertility to their mothers (Dworkin-McDaniel, 2011).

The impact of infertility may also have more consequences than just for individuals: There is mounting concern regarding the contribution of infertility to the sub-replacement fertility levels being experienced in many middle to high-income countries. So called sub-replacement fertility occurs when the total fertility rate (TFR), the theoretical average total number of live born children per woman in a population (calculated using the population's current age-specific fertility rates), falls below the population replacement level (generally accepted to be a TFR of 2.1 in middle to high-income countries).

Figure 1.1 displays the TFR for selected Organisation for Economic Co-operation and Development (OECD) countries from 1980–2012.



Data sourced from Gapminder (2014) and Statistics New Zealand (2013b).

Figure 1.1: The total fertility rate of selected OECD countries, 1980–2012

From 1980–2012, New Zealand and the United States of America (USA) were the only countries amongst these selected OECD countries that had a TFR that reached replacement level. In 2009, no country in the European Union and only a few of the transitional and developed Asian countries had replacement level fertility (United Nations, 2011). In the USA, the TFR is not as depressed as in many other high-income countries, nonetheless it has been estimated that the TFR could have been reduced by as much as 10% due to infertility resulting from delayed childbearing (Morgan and Hagewen, 2005). However, there are differing perspectives on whether sub-replacement fertility is a negative phenomenon. While this would certainly be the case for pro-natalist societies (Surkyn *et al*., 2008), for those wishing to achieve greater environmental stability a low TFR may be favourable. From a more global perspective a reduced TFR is more likely to be sustainable, and countries such as New Zealand could achieve net population growth through migration rather than an increased TFR.

1.4 The determinants of infertility

Porta (2008) describes a risk factor or determinant as: 'An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that, on the basis of scientific evidence, is known to be associated with meaningful health-related condition(s)'. Determinants often act jointly in relatively long and complex processes; they may be directly or indirectly associated with the outcome (Porta, 2014). Proximal determinants are factors that are generally closely associated with the outcome of concern. Distal determinants are the upstream factors, generally the social, political and economic environment, that often act globally. These predispose individuals to the intermediate determinants that directly cause the proximal determinants.

Figure 1.2 lists examples of the main distal, intermediate and proximal determinants of infertility risk. Whilst the relationship between these various determinants is complex, and not always fully understood, a simplistic example can be given using ovulation disorders: Low socio-economic status (SES) is associated with many negative outcomes, including higher levels of smoking which

accelerates depletion of ovarian follicles (which can cause earlier menopause) (The American Society for Reproductive Medicine, 2008). Depleted ovarian follicles increase the risk of ovulation disorders and subsequent infertility.

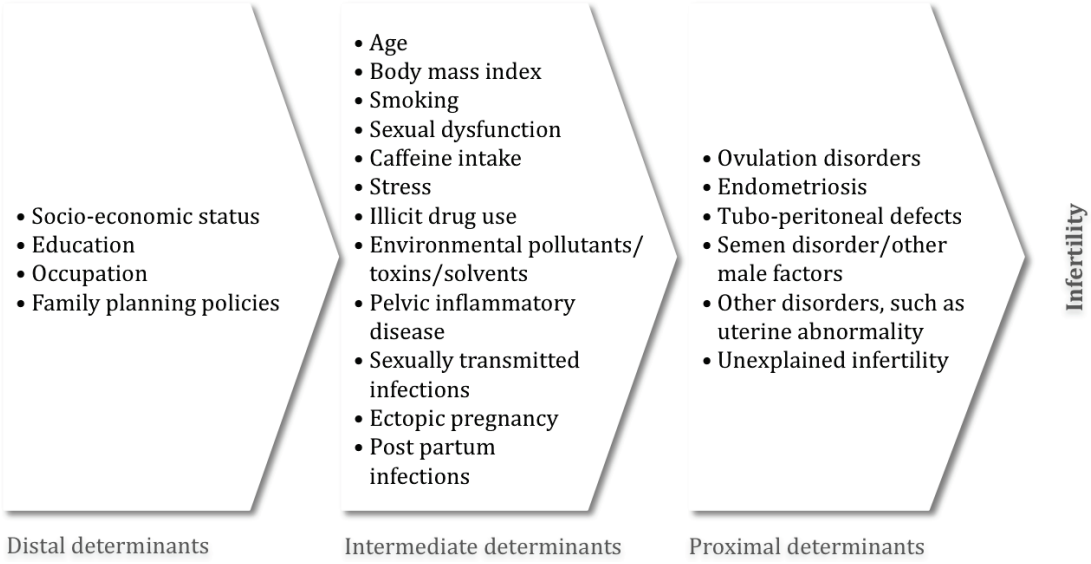


Figure 1.2: The determinants of infertility risk

1.4.1 The proximal determinants of infertility

Typically, the proximal determinants of infertility risk are grouped into five categories: Ovulation disorders, which includes polycystic ovary syndrome (PCOS); endometriosis; tubo-peritoneal defects (any condition of the fallopian tube, ovary or other pelvic structure that distorts the functional anatomy except endometriosis); semen disorder or other male factors; and other factors (e.g. uterine abnormalities). Unexplained infertility is also a diagnostic category; this diagnosis is only made when infertility investigations have been completed and no known cause found and is distinct from infertility where the cause is not known and a complete investigation has not been undertaken.

1.4.2 The intermediate determinants of infertility

Intermediary factors are potentially the most readily modifiable determinants of risk in terms of infertility prevention targets. Intermediate determinants that increase the risk of infertility include: Increasing maternal age; paternal age

greater than 50 years (Baird *et al.*, 2005); a very low or very high body mass index (BMI); smoking; sexual dysfunction; excess caffeine intake; increased stress; illicit drug use; and exposure to environmental pollutants/toxins/solvents (The American Society for Reproductive Medicine, 2008). Intermediate determinants for tubo-peritoneal defects may also include: A prior history of pelvic inflammatory disease (PID); some sexually transmitted infections (STI); ectopic pregnancy; and post partum infections.

There is a strong relationship between fertility and age, particularly for women. In their twenties women having regular unprotected intercourse have a 25% chance of conception each menstrual cycle, by age 35 years this chance halves and by age 39 it halves again (Menken *et al.*, 1986, Taylor, 2003, Baird *et al.*, 2005). A substantial portion of this age-related fertility decline is likely to be explained by increasing chromosomal abnormalities in oocytes with age (Munné *et al*., 2007). A study using samples from patients undergoing fertility treatment reported that 50–75% of oocytes are chromosomally abnormal (Wilton, 2005). The proportion of abnormal oocytes increases dramatically after age 35 years, resulting in lower pregnancy rates and higher miscarriage rates (Baird *et al.*, 2005). This increase in abnormality with age possibly explains the finding by Maheshwari *et al*. (2008) that the diagnosed cause of infertility is associated with age, with higher proportions of unexplained infertility in women over the age of 35 years.

Considering other intermediate factors, Hassan and Killick (2004) reported that being obese (a BMI of 35kg/m^2 or more) was associated with a doubling of the time to pregnancy, and being underweight (a BMI of less than 19kg/m^2) with a quadrupling of this. A systematic review and meta-analysis found that the odds of infertility in women were 60% higher for smokers compared with non-smokers (Augood *et al.*, 1998). There has been some debate over the role of excess caffeine intake and stress in increasing time to conception, with the most recent evidence suggesting that they both increase the risk of infertility (Bolumar *et al.*, 1997, Lynch *et al.*, 2014).

1.4.3 The distal determinants of infertility

The more distal overarching risk determinants for infertility, similar to many health outcomes include SES, education, occupation and the social climate and policies, particularly those relating to family planning. These factors act globally on many of the intermediate determinants of infertility. Education is important as it acts directly on the age of childbearing; in middle to high-income countries, higher levels of education are associated with higher levels of infertility through the postponement of childbearing (Callister and Didham, 2007, Terava *et al.*, 2008, van Roode, 2010). The role of policies to promote childbearing/increase fertility, such as cash incentives, subsidised childcare and paid maternity leave, have been debated, however, there is little evidence for policies that increase fertility (Crosignani, 2010). Nevertheless, there is evidence that there are policies that can decrease fertility, for example lack of provisions for maternity leave and child care support for women employed outside the home (Callister and Didham, 2007). Occupation influences decisions about postponement of childbearing as well as being a potential avenue for occupational exposure to chemicals that could be hazardous to fertility, in particular men's sperm counts may be adversely affected by exposure to toxins (Oliva *et al.*, 2001).

1.4.4 Geographic variation in the determinants of infertility

The predominant determinants of infertility risk vary strongly by geographic region. Of those determinants listed in Figure 1.2, the main identified determinants in middle to high-income countries are increasing age, endometriosis, obesity and higher educational level (Terava *et al.*, 2008, Bhattacharya *et al.*, 2009, Herbert *et al.*, 2009b). *Chlamydia trachomatis* is the most commonly diagnosed STI in New Zealand (The Institute of Environmental Science and Research Ltd., 2012) and many other high-income countries; it has the potential to cause PID, ectopic pregnancies and tubal factor infertility. However, only a small effect from *C. trachomatis* has been found; overall there is little evidence for any substantial burden of infertility due to STIs in middle to high-income countries (Wallace *et al.*, 2008, Bhattacharya *et al.*, 2009, Herbert *et al.*, 2009b, Kavanagh *et al.*, 2013). This

may be because STIs are generally much less common in high-income countries and many of these countries have policies and/or formal screening programmes for detection and treatment of *C. trachomatis* (Wallace *et al*., 2008, Bender *et al*., 2011). Furthermore, *C. trachomatis* infection is often asymptomatic and can self-resolve, therefore, past infection may not be recognised amongst women with tubal factor infertility. It has also been suggested that the proportion of *C. trachomatis* infections that progress to severe reproductive sequelae may have previously been over-estimated (Low *et al*., 2006).

In many low-income countries, particularly in sub-Saharan Africa and Thailand, the main determinants of risk include the intermediate factors of STIs and other reproductive tract infections, unsafe birthing/abortion practices, and the distal factor of low literacy (Adetoro and Ebomoyi, 1991, Schrijvers *et al.*, 1991, Mohsen *et al.*, 2001, Geelhoed *et al.*, 2002). These risk determinants are commonly associated with tubal factor infertility and secondary rather than primary infertility, as the process of having an abortion or a birth increases exposure to these determinants. However, there is evidence of age-related infertility in some low-income countries, with very young age of first coitus/marriage, probably due to intercourse occurring before menarche, along with older ages posing an increased risk of infertility (Koetsawang *et al.*, 1985, Schrijvers *et al.*, 1991, Mohsen *et al.*, 2001, Safarinejad, 2007).

1.5 Treatment

Assisted reproductive technology (ART) procedures comprise any technique that includes the *in vitro* handling of both human oocytes and sperm, or embryos, for the purpose of establishing a pregnancy, the most recognised of these procedures being *in vitro* fertilisation (IVF) (Zegers-Hochschild *et al.*, 2009). IVF is sometimes performed in conjunction with direct injection of sperm into an ovum (intra cytoplasmic sperm injection [ICSI]); this can lead to better outcomes for couples where sperm quantity/quality is an issue. Other variations of ART (and IVF) include the use of donor eggs or sperm (or both), the use of a surrogate mother to carry the pregnancy and less commonly known/used procedures such as gamete

transfers. Overall, with improving screening of potential IVF recipients and improved technology and techniques, live birth rates of over 40% amongst women aged 35 years or younger have been reported after the use of all embryos from an IVF treatment (Lintsen *et al.*, 2007, Advisory Committee on Assisted Reproductive Technology, 2014).. In New Zealand, ART is legally defined by the Human Assisted Reproductive Technology Act 2004 (Ministry of Justice, 2013); therefore, the definition of ART is broader (it includes donor insemination [DI]) than the previously mentioned internationally recognised definition. The most common DI method uses intra-uterine insemination (IUI). Common alternatives to ART procedures include gynaecological surgery and ovulation induction (OI) drugs to promote/correct ovulation. Non-treatment interventions may also be recommended, such as advice/programs to manage women's BMI and for smoking cessation.

Whilst treatment options are available, treatment may be invasive and also carry a high cost to both individuals and the health system. In New Zealand, the cost of a full IVF treatment cycle starts at $NZ9,900 depending on the techniques used and the amount of drugs required (Fertility Associates, 2014). Public funding for infertility treatment in New Zealand is restricted to a maximum of two cycles of IVF in a couple's lifetime, and then is only available if stringent eligibility criteria are met. These criteria include the woman being aged 39 years or younger, having a suitable BMI (not being underweight or obese) and being a non-smoker. Women/couples are further assessed for eligibility based on the severity of their diagnoses and *social deservedness*, e.g. couples lose points if they already have children, but gain points for longer periods of infertility (Gillett and Peek, 1997, Peek, 2006, Gillett *et al.*, 2012). New Zealand has lower rates of children born with the assistance of reproductive technology than many other industrialised countries (Mansour *et al.,* 2014), in part due to these restrictive funding criteria (Peek, 2006).

1.6 Fertility and infertility in New Zealand

In New Zealand, for the past 20 years, the TFR has been relatively stable at around two live births per woman, with the rate currently at 2.1 (Statistics New Zealand, 2007b, Statistics New Zealand, 2013b). This TFR is relatively high compared with most other countries in the OECD (refer to Figure 1.1 on page 5) (OECD, 2004). However, modelling based on education, employment and recent fertility trends suggest that there is a possibility that the TFR in New Zealand may reduce in the future (Callister and Didham, 2007).

Fertility and education/employment have traditionally being viewed as alternative choices for women (OECD, 2001). Education and career development have been cited as contributing to the postponement of childbearing (Terava *et al.*, 2008, van Roode, 2010), and as such are distal determinants of infertility. Certainly having children is a significant financial cost, which may also contribute to postponement decisions. A recent cohort study, 'Growing up in New Zealand', that is following families and their children from pregnancy, found that around half of all families reported hardship in their infant's first year, with many families suffering a significant and challenging decrease in income (Morton *et al.*, 2010, Morton *et al.*, 2012). In 2009, New Zealand's Inland Revenue Department calculated that the cost of a child is around NZ$250,000 from birth to age 18 years. This, however, might underestimate the true cost as it does not include those things not considered basic costs, such as childcare and dental treatment, nor opportunity costs (Inland Revenue New Zealand, 2010).

There has been a strong trend since 2005 towards increased employment rates in women aged 20–39 years in New Zealand and increases in childlessness amongst women aged 25–44 years, particularly within the growing proportion of more highly educated women (Callister and Didham, 2007). In 2006, over 40% of women aged 25–44 years with a university level qualification were childless compared with less than 20% of women with no qualification. Further differentiation by women's intention to remain childless could not be provided in this study due to data source limitations. To maintain the TFR at around 2.1, this

would then suggest that there is polarisation in fertility patterns, such that amongst sub-population groups there are opposing trends with some women having families of more than two children whilst others are remaining childless (Pool *et al.*, 2007).

Polarisation is also seen in the age at which women are having children: When compared with most western European countries and Australia, New Zealand has relatively high rates of teenage pregnancy despite the gradual declines seen from 2008–2014 (refer to Figure 1.3) (Kukutai, 2014).

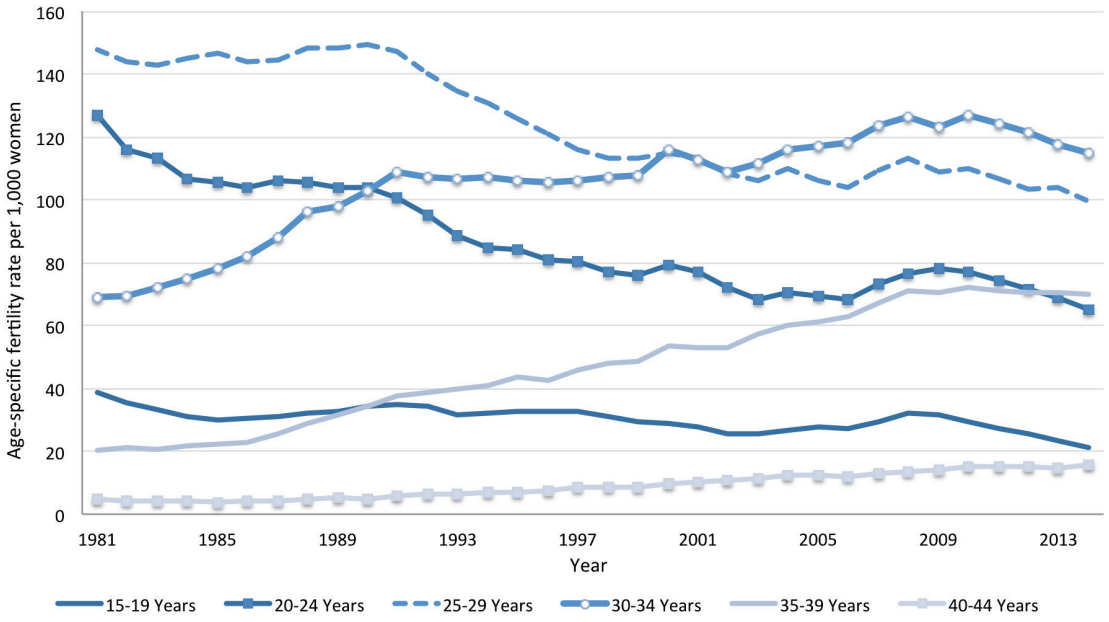


Figure reproduced from Kukutai (2014).

Figure 1.3: Age specific fertility rates in New Zealand women, 1981–2013

Yet, overall in New Zealand there has been a strong shift to older childbearing. In the 1960s the median age of New Zealand mothers was 26 years, in the 1970s this dropped to less than 25 years, it then climbed to reach 30 years in the 1990s and has been relatively stable since then (The Families Commission, 2008). The main reasons cited for this trend have been financial security and the longer time spent in higher education (especially by women).

Along with this shift towards later childbearing in those women who choose to have children, the 2006 New Zealand Population Census also showed that 16.7% of women born in 1966 had not had children (Boddington and Didham, 2009). But

for those born just ten years later, in 1975, indications are that up to a quarter may remain childless throughout their reproductive lives (Statistics New Zealand, 2012). It is possible that these predicted increases in childlessness could be at least partially due to underlying increases in infertility due to delayed childbearing.

Parallel to the shift towards older childbearing, the age of first coitus declined markedly to a median of 16 years in women in the latter half on the twentieth century (Dickson *et al.,* 1998), but appears to have been relatively stable since then (Psutka *et al.,* 2012). These two trends have increased the time period in which women (and men) are exposed to infections that can potentially impair fertility.

Based on clinical data from some of New Zealand's North Island fertility clinics, it appears that the increasing delay in childbearing has already caused fertility problems for a significant number of New Zealand women (Peek, 2006, Sceats, 2006). Further to this, data from the Dunedin-based Otago Fertility Service (OFS) indicate an increasing use of specialist fertility services. In the nine-year period 1986–1994 there were 1,330 women evaluated by the OFS, and subsequently in the eight years from 1998–2005, 1,438; an increase in annual service use of just over 20% between these two periods. While this does not take into account changes in the size/structure of the population in the region during this period; these changes are unlikely to account for these differences. Along with increased service use, the increase in the age of childbearing, as well as the effects of increasing obesity, were evident. In the latter period, 37% of women referred were over 35 years, 10% over 40 years, and 21% had BMI greater than 30 kg/m^2 (Gillett, 2007).

The only estimate of the number of people provided with infertility services in New Zealand comes from a 1995 report on the 'Costs and Effectiveness of Infertility Services in New Zealand', an analysis conducted for the Core Health Services Committee of the New Zealand Department of Health (now the Ministry of Health). In this report it was estimated that 3,500 new referrals were made for infertility services in New Zealand annually, of which 68% of would proceed to treatment (Core Services Committee, 1995). Reports are available on the uptake and success of ART in New Zealand, but these reports do not provide data on

untreated women attending fertility clinics (Advisory Committee on Assisted Reproductive Technology, 2014). A recent burden of disease study reported that, in New Zealand, reproductive disorders accounted for 17% of all health loss for women aged 15–44 years, ranking second only to mental health disorders (Ministry of Health, 2013). Unfortunately the proportion of this reproductive health burden that was due to infertility was not estimated because of a lack of reliable data.

One New Zealand based mixed methods (qualitative and quantitative) study specifically examined infertility from a Māori perspective, conducting in-depth interviews with 74 participants (Reynolds and Smith, 2012). While not able to provide statistical evidence of the burden of infertility amongst Māori, the study highlighted the importance of fertility (and infertility) and how common stereotypes and expectations add to the difficulty of coping with infertility for Māori. The authors also highlight concern, that despite the younger median age of first birth in Māori compared with non-Māori, Māori have higher levels of exposure to fertility risks such as smoking and obesity; this suggests that the burden of infertility in the Māori population needs further investigation.

Currently, there are little population-based data available in New Zealand to compare with these clinical data. The information available is limited to two surveys, both based on convenience samples. A health magazine undertook one survey among its readers, which included questions regarding infertility experiences and attitudes (O'Brien, 2012). The other study was mainly an attitudinal survey (Labett, 2005), this was commissioned by Fertility New Zealand, an organisation that provides advocacy and support for people with infertility. The magazine survey concluded that 17% of women had taken longer than 12 months to conceive their *first* child. This measure underestimates the number of women who experienced infertility in this sample, as it includes only primary infertility, and excludes the amount of time trying for any subsequent children and women who could not conceive a desired child at all. Knowledge and attitudes data from these studies indicated that despite demographic trends in New Zealand, women had traditional values regarding family formation and having children, but poor

knowledge regarding the risk of infertility posed by delayed childbearing and age-related fertility declines. The survey respondents generally ranked their income, career and relationship status as more important than their age when deciding to have a child. Women aged in their thirties were just as optimistic about their future fertility as women in their twenties.

1.7 Summary

The experience of infertility can have a major impact on individuals, families and relationships, as most people have life plans that involve children. In addition, it can result in a considerable cost to both individuals and health services. An international review of infertility, based on the most commonly used definition of ever *trying to conceive for 12 months or more without success or seeking medical care to get pregnant*, found that the experience of infertility was just under 10% (Boivin *et al.*, 2007). This review found that around half of these couples had not sought medical care. However, due to difficulties in interpreting infertility literature, particularly the substantial variation in definitions of infertility, conclusions about the burden of infertility and service provision must be interpreted cautiously.

The aetiology of infertility is complex, with many factors affecting an individual's risk of infertility. However, clearly age is an important determinant, especially for women, with increasing age strongly correlated with decreasing fertility for women older than 30 years. Due to social changes over the past few decades, many women/couples in New Zealand are delaying the start of their families, with the median age of childbearing now around 30 years. In conjunction with this trend to delay childbearing, there has been a drop in the average age of first sexual intercourse resulting in a longer period where fertility can be compromised by STIs,

Consequently, it seems likely that the number of women experiencing infertility will increase. There is some evidence to support this; between 1986 and 2005 the OFS saw an increase in annual service use of about 20%. It was also noted that

there was a substantial number of patients over the age of 35 years and with high BMIs. Because treatment success declines with increasing age and BMI, and publicly funded treatment is only available for women under 40 years with a BMI less than 32 kg/m^2, more couples may need to undergo extensive, expensive or ultimately unsuccessful privately-funded treatment at considerable personal cost.

National data on infertility treatment are limited to the numbers of ART and DI procedures undertaken annually and the outcome of these procedures (Advisory Committee on Assisted Reproductive Technology, 2014). The number of women/couples who might benefit from fertility services, but have not attended, cannot be ascertained. Moreover, there are differences in age patterns of births by factors such as SES, occupation and location (Statistics New Zealand, 1997), suggesting there may be differences in infertility, and use of services by these factors. Furthermore, despite the importance of this to women's health especially, knowledge of women's understanding of infertility and possible success of treatment is limited. However, the studies that have been done suggest this is both incomplete and optimistic (Adashi *et al.*, 2000, Labett, 2005).

1.8 Identified knowledge gaps and research opportunities

A better understanding of the prevalence of infertility in New Zealand, and the health seeking behaviours and use of services offered to women/couples with infertility, is required. Research undertaken to fill this knowledge gap would also provide an indication of unmet service need. Information about women's perceptions around infertility and related treatment is also essential; this will indicate whether they have appropriate knowledge to make informed decisions.

Therefore, this research project, focused on the Otago and Southland regions of New Zealand, could be used to gain a unique insight into infertility in New Zealand, and be used to lay the groundwork for further research on infertility within New Zealand. In particular, this work will be able to inform a more extensive national study of infertility that should examine infertility patterns among Māori, Pacific and other ethnicities (the Māori and Pacific populations in Otago and Southland

are relatively small compared with North Island regions). Women/couples from these ethnic groups might have differing infertility determinants and less access to treatment. The sexual and reproductive health component of an on-going health survey that is currently being undertaken will potentially contribute to this broader understanding of infertility in New Zealand.

The specific aims of this thesis are presented at the end of the more comprehensive review of the literature in Chapter Two.

1.9 Thesis structure

Chapter One has provided an introduction to infertility, its importance and trends nationally and internationally. This provides a context to examine information gaps and the overall objectives of this thesis.

Chapter Two will review the literature on the prevalence/cumulative incidence of, and service use for, infertility, as well as literature on fertility knowledge. The specific aims for this thesis are set out at the end of this chapter.

Chapter Three will outline Study One: A population-based cross-sectional study of infertility, service use and knowledge amongst women resident in Otago and Southland (two regions in the lower South Island of New Zealand). This chapter includes Study One's objectives, methods and results.

Chapter Four will outline Study Two: An analysis of the OFS dataset. The OFS is the main provider of secondary and tertiary specialist services for infertility in the Otago and Southland regions. This chapter includes Study Two's objectives, methods and results.

Chapter Five will provide a brief analysis comparing related findings from the population and clinic-based infertility studies, and discuss the similarities and differences in the findings of the two studies.

Chapter Six will outline Study Three: A feasibility study on the utility of hospital discharge data on publicly funded admissions for infertility, pelvic inflammatory disease and ectopic pregnancy for monitoring infertility and indicators of tubal factor infertility nationally. This chapter includes an introduction and literature review, and the objectives, methods and results of this study.

Chapter Seven will summarise and discuss the results of the three studies, compare the findings with the international and national literature, examine the relative strengths and limitations of the studies in this thesis, conclude on the importance of its findings, health care provision and policy implications, and consider future directions for research.

CHAPTER TWO:

REVIEW OF THE INFERTILITY LITERATURE

Chapter Two reviews the literature on the prevalence and/or cumulative incidence of, and service use for, infertility, as well as fertility knowledge and attitudes. The specific aims for this thesis are set out at the end of this chapter.

2.1 Introduction

Having a comprehensive understanding of the prevalence/lifetime (cumulative) incidence of infertility is important in order to gauge the magnitude of the issue, the likely impact on individual health and population dynamics, and plan for the allocation of health resources. There is little information available regarding the extent of infertility issues in New Zealand and it is possible that recent studies based in countries such as Scotland and Australia are not generalisable to the whole New Zealand population; New Zealand has a large indigenous (Māori) population, and considerable migrant populations from the Pacific Islands. These groups within New Zealand have very different fertility patterns; these differences could influence the levels and types of infertility seen in these populations.

In order to design, analyse and interpret the data from a much needed population-based study of infertility, service use for infertility and knowledge about infertility in New Zealand, it was necessary to examine the study designs employed, with their relative strengths and limitations, and results obtained in other countries (this current review was undertaken before Gurunath *et al.* (2011) published an extensive review on infertility definitions and prevalence). Additionally data from clinic-based studies reporting the diagnoses, uptake of treatment and outcomes for women with infertility were considered useful to compare the relative burden of disease and service use estimates, and because following on from analysing population-based infertility data, the clinic-based data from the same region were to be analysed and compared.

As the New Zealand population has shown polarisation in its fertility pattern, and, that some disease patterns, such as for rheumatic fever, are for Māori similar to many lower income countries (Wilson, 2010, Milne *et al.*, 2012), it was considered that the literature from both middle to high-income and low-income countries should be reviewed.

2.2 Aims

This chapter reviews the available literature on the methods and results from epidemiological studies of:

- Infertility prevalence and/or incidence in representative population-based studies of women (or men and women if women's data are reported separately).
- Service access for infertility and outcomes with or without treatment (from representative population-based studies and clinical settings).
- Knowledge and attitudes regarding infertility (from representative population-based studies).

The predominant methods used, the quality of the studies, and the study findings are described.

2.3 Methods

Searches for academic articles were primarily conducted in PubMed and Google Scholar. For PubMed the search was limited to the abstract or title, in humans and in English. There were no date limitations applied; with the last date a search was conducted being 27 April 2011 (although some citations were examined after this date). The following search terms were combined with infertility: Epidemiology; prevalence; incidence; trends; service; knowledge; and attitudes. To further identify possible sources of information on infertility in New Zealand a general internet search (using Google) was also conducted combining the keywords New Zealand and infertility, with: Prevalence; incidence; rates; and trends. Articles

were exported to an EndNote X6 database and abstracts screened to identify relevant articles to evaluate in full. Citations and references were also examined to identify further studies inclusion in these relevant articles. Articles identified for full evaluation were assigned to one or more of three groups depending on their content (some articles had content that related to more than one of the review topics); either 'Infertility prevalence studies' and/or 'Infertility service use and outcomes' and/or 'Infertility knowledge and attitudes'. Studies in these three groups were evaluated to determine inclusion in the three-part literature review.

2.4 Results: Included studies

Figure 2.1 on the next page details the evaluation process to determine the inclusion of studies in the three-part literature review.

After the initial search, 221 papers were identified and screened by abstract only. Following screening 119 papers were excluded, and 102 papers sorted into at least one topic area for full evaluation. A further 20 papers and two peer-reviewed conference proceedings were added and sorted into topic areas after reviewing references and citations in those studies that were evaluated for inclusion in at least one of the review topics (giving a total of 124 studies evaluated).

Sixty-five papers were identified for evaluation on the prevalence and/or incidence of infertility. Thirty studies were then excluded and the remaining 35 were included in the review. Sixty-one papers were identified for a full review on the service use for infertility. Inclusion criteria were clinical or population-based studies that measured service access, treatment provision and/or outcomes after service use. Thirty-one studies were then excluded and the remaining 30 included in the review, this incorporated 21 studies that were also included in the review of infertility prevalence. Twenty-one papers were identified to review on fertility knowledge and attitudes in the general population. Nine studies were then excluded and the remaining 12 studies included in the review; one of these incorporated studies had also been included in the review of infertility prevalence.

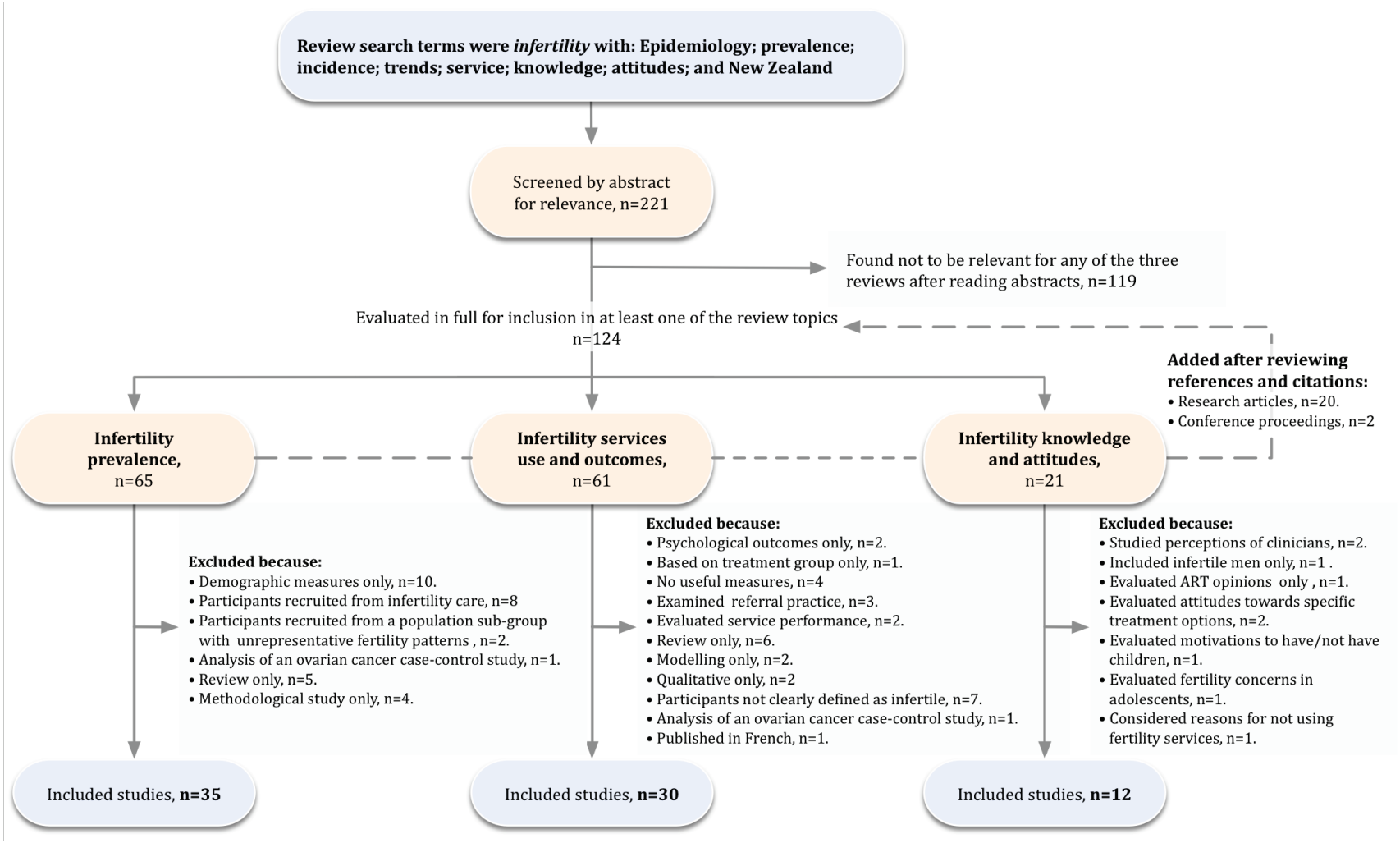


Figure 2.1: The evaluation process for inclusion of studies in the three-part literature review

2.5 Methods and methodological issues

The methods and limitations of all studies included in this three-part review were assessed in order to provide a more comprehensive understanding of the results and provide an evidence-base for the design of the population-based study of infertility in Otago and Southland. Further assessment of the methods can be viewed in Appendix A from page 307.

2.5.1 Studies measuring the prevalence of infertility

Study design

All studies identified were cross-sectional surveys; two of these were nested in a large birth cohort study of just fewer than 6,000 women (the Australian Longitudinal Study on Women's Health) (Herbert *et al.*, 2009a, Herbert *et al.*, 2009b). Resulting from the universal employment of cross-sectional methods, there were two possible infertility measures provided: The current prevalence and/or the cumulative incidence of infertility over the lifetime (refer to Table 1.1 on page 3 for more information on infertility definitions and terms).

Almost all studies were carried out with face-to-face interviewing or postal questionnaires on randomly selected population-based samples. Three studies used computer aided telephone interviews (CATI) (Greil and McQuillan, 2004, Clark and Mackenzie, 2007, Slama *et al.*, 2008); by necessity these studies were limited to women with a landline telephone and were, therefore, not truly representative of the population. As not all women have access to this, it was likely that the most disadvantaged members of the population were not included in the sampling frame. One study had a random sample of college alumnae, so is also not likely to be representative of the whole population (Wyshak, 2001).

Definition of infertility

There was considerable variation in the definition of infertility used in the reviewed studies. The most recent accepted epidemiological and clinical definition, as mentioned earlier, is attempted to conceive for 12 months or more, using the

specific wording *trying* and often referred to as *trying times* (Larsen, 2005, Gurunath *et al.*, 2011). However, the World Health Organization has published a variation of this definition which is more encompassing, being 12 months or longer of regular unprotected intercourse without conception (Zegers-Hochschild *et al.*, 2009). Most studies have used variations of these two definitions, although some use a two-year duration, which was historically more common.

Some studies such as that conducted by Wyshak (2001), had results that were not inclusive of all infertile women; in this study they did not consider women who eventually had a non-treatment related pregnancy as meeting their definition. Inconsistencies such as this exclusion of some infertile women from the numerator can make direct comparisons of infertility results derived from seemingly the same definition difficult. Therefore, for the purpose of this review, these studies that had not included all infertile women in their numerators were re-calculated with the available information so they were inclusive of all women who were infertile (studies where this was not possible were already excluded from this review).

Denominator for calculating infertility prevalence

Many studies had a sampling frame that included either all women or married women, which was used for the denominator for calculating the prevalence of infertility (refer to Tables 2.1 on page 37 and 2.2 on page 42 for details of denominators used for each reviewed study). However, as not all of these groups of women would have been at risk of infertility, this will lead to the prevalence of infertility being underestimated. Schmidt *et al.* (1995) showed in their study that including all women in the denominator substantially reduced the measured prevalence of infertility from 26.2% to 15.7%; the denominator differences were most noticeable in women under the age of 35 years. A more appropriate denominator has been argued to be women who have either conceived or have tried to conceive when using the time spent trying definition (Gurunath *et al.*, 2011); a number of studies used this approach.

Limitations and sources of error

The strengths of cross-sectional designs are that they provide useful measures of infertility in a cost-effective and timely manner. Prevalence measures are adequate for deriving information on trends and population burden, which is in turn useful for assessing current and future service needs. Despite the strengths of cross-sectional designs, weaknesses exist such as recall bias, interviewer bias, response rate issues and temporal sequence issues (this is important when trying to establish causation).

Recall bias is an issue with cross-sectional study design that is of particular importance for studies on fertility (and, therefore, infertility), particularly if measuring the cumulative incidence, because this requires detailed recall of events which may have occurred many years earlier, these events may no longer be salient (e.g. the exact length of time it took to get pregnant). However, there have been methodological studies looking at fertility histories and fecundity data that suggest that recall of up to 20 years can be accurate and valid (Baird *et al.*, 1991, Zielhuis *et al.*, 1992, Joffe *et al.*, 1995). Nevertheless, incomplete recall cannot be ruled out. Two further issues, a lack of incidence data and temporal sequence (which both result from cross sectional studies being used to measure the prevalence of an outcome and/or risk factors at a single point in time without follow up over-time), reduce the utility of surveys for identifying potential causes of infertility.

Low response rates are now common in cross-sectional studies and can be a limitation. Whilst comparisons can be made with demographic factors in the population to determine representativeness, there is very little information that can be used to determine how these low response rates have influenced the prevalence measure in infertility studies. Response rates in the reviewed studies ranged from 46–100%. Generally response rates were better in low-income countries and in studies employing face-to-face interviewing (refer to Tables 2.1 and 2.2). In middle to high-income countries, there was a general downward trend in response rates over time, particularly for postal surveys. Postal surveys in England in 2001 (Oakley *et al.*, 2008) and Scotland in 2007 (Bhattacharya *et al.*,

2009) achieved response rates of 46% and 50% respectively, whereas surveys in these countries up until 1995 all achieved response rates over 75% (Templeton *et al.*, 1990, Gunnell and Ewings, 1994, Buckett and Bentick, 1997).

Little information was given by the majority of the reviewed studies on whether common methods to improve response rates such as lottery style incentives, recognition of time taken to participate (monetary or otherwise) and repeat contacts were employed. Bhattacharya *et al*. (2009) contacted participants twice in their postal survey; this did improve their response rate from 37% to 50%. Two earlier postal studies in England provided more detailed information on follow up of non-responders; this included matching names and addresses to the telephone book and calling non-responders. This approach resulted in a good improvement from a response rate of 55% to 85% in one study and 54% to 86% in the other study (Templeton *et al.*, 1990, Buckett and Bentick, 1997). It is notable that even at this time, Templeton *et al.* (1990) reported that of the 208 non-responders they looked up in the telephone directory, they were able to make phone contact with only two-thirds, of whom less than a half took part in the survey; therefore in their next study amongst a younger cohort they did not employ telephone follow up (Templeton *et al.*, 1991).

2.5.2 Studies evaluating service use for infertility

Population-based epidemiological studies of infertility service use

Many cross-sectional surveys on infertility included measures of service access and a few also looked at treatment provision and outcome. Unfortunately, most studies that investigated service use in low-income countries were based on fecundity measures and were, therefore, not able to be included in the literature review, resulting in only one population-based study from a low-income country.

Service access was measured using varying definitions. Some studies specifically asked about access to medical services, but the level of access (primary, secondary or tertiary service) was either not specified, or varied between these studies. Two studies specified the level of access to medical services and were, therefore, able to

look at proportions of women being referred to more specialist services (Gunnell and Ewings, 1994, Buckett and Bentick, 1997). Some studies did not specify how service access was measured or defined (Clark and Mackenzie, 2007), and had very non-specific questions such as that used by Herbert *et al*. (2009): 'did you seek advice/treatment?' (Herbert *et al.*, 2009b).

Treatment uptake was not possible to compare between these studies as what was included as *treatment* was diverse and in one case the definition of treatment was not specified at all (Herbert *et al.*, 2009a). Also, only three epidemiological studies gave an indication as to whether the infertility was spontaneously resolved, resolved following treatment or unresolved (Schmidt *et al.*, 1995, Buckett and Bentick, 1997, Bhattacharya *et al.*, 2009).

Clinic-based epidemiological studies of infertility service use

All but one of the studies were based on an analysis of routine records held by general practitioners (GP) and/or tertiary infertility services (refer to Table 2.3 on page 56). Studies based in a clinical setting have the disadvantage of not being able to give information about the proportions of infertile women who access services, but have the advantage of providing information on diagnoses, treatment and outcomes free from issues such as recall bias.

2.5.3 Studies evaluating infertility knowledge and attitudes

Most of the reviewed knowledge surveys were amongst academics or students. One study, however, was a population-based survey of childless women (Daniluk *et al.*, 2012), and two were population-based samples covering a wide range of ages (Adashi *et al.*, 2000, Clark and Mackenzie, 2007). There were a further two knowledge surveys amongst women attending clinics for infertility services (Blake *et al.*, 1997, Vause *et al.*, 2009). These studies used a variety of survey methods such as internet surveying, face-to-face interviews, postal surveys and telephone interviewing.

Most knowledge and attitude surveys included used different survey instruments, however core areas of enquiry were evident: The definition of infertility and

infertility levels in the population; the timing of the fertile window; the likelihood of conception in a fertile couple; the likelihood of treatment success; and whether fertility is influenced by alcohol, smoking, drugs, BMI, STIs and age.

In general, these studies were not explicit about recruitment or sample size calculations, and often did not report response rates. Therefore, whether these studies were likely to be representative of the target population was unable to be determined.

2.6 Results: Studies evaluating the prevalence of infertility

Of the 35 studies reviewed estimating the levels of infertility, 23 were in middle to high-income countries (Table 2.1 on page 37) and 12 studies in low-income countries (Table. 2.2 on page 42). The studies in these tables are grouped by infertility definition and then ordered chronologically according to the year the study was conducted, starting with the most recent study.

2.6.1 Levels and patterns of infertility in middle to high-income countries

Lifetime cumulative incidence of infertility

Of the 35 studies reviewed for infertility prevalence, 23 were in middle to high-income countries, and the majority of these provided an estimate of the lifetime cumulative incidence of infertility. Lifetime estimates of 12-month infertility ranged from 4.8–33.8% (refer to Table 2.1). Of studies conducted since 2000 amongst women of reproductive age (ranging from 28–50 years old), estimates of lifetime infertility (as determined at the age the participant completed the survey) were relatively similar with measures of 17.3%, 17.5%, 19.9% and 21.2% in Scotland, Australia, Finland and the USA respectively (Greil and McQuillan, 2004, Bhattacharya *et al.*, 2009, Herbert *et al.*, 2009b, Klemetti *et al.*, 2010). Another study in Finland in 2002 using the broader age range of 24–64 years gave a measure of 16.0% (Terava *et al.*, 2008). There were similar results from two other studies with measures of 16.7% (Australian women aged 18 years and over) and

17.1% (French women aged 18–60 years) (Clark and Mackenzie, 2007, Slama *et al.*, 2008). These studies all used a definition of 12 months or more attempting to conceive without success.

Those studies using 12 months or more of unprotected intercourse as the definition of infertility had higher estimates of infertility ranging from 6.6–33.8%. Earlier studies tended to use the unprotected intercourse definition (Webb and Holman, 1992, Gunnell and Ewings, 1994), or a longer time period for infertility (Templeton *et al.*, 1990, Templeton *et al.*, 1991). Another study that did employ the 12 months trying to conceive definition, in the Netherlands in 1992, measured infertility at 10.7%, but this appears to have been limited to primary infertility only (van Balen *et al.*, 1997).

Norwegian infertility measures, from surveys in 1985 and 1995, were unusually low: 4.8% for the lifetime estimate of 12 months trying to conceive and 1.8% for involuntary childlessness (Rostad *et al.*, 2006), although this study was amongst women of an older age than most other studies (50–69 years). However, Sundby and Schei (1996) conducted an earlier study in the neighbouring area of Norway and also had a low lifetime estimate of 12 months trying to conceive of 10.3%, this was amongst women aged 40–42 years.

All together there were 11 studies that included women in the reproductive age range (arbitrarily less than 50 years old), and measured the cumulative incidence of primary and secondary infertility (12 months of more trying to conceive).

For the purpose of this review, these studies were analysed using the Microsoft Excel method for meta-analysis supplied by Neyeloff *et al*. (2012). Overall, amongst these studies, the weighted average for lifetime experience of infertility was just under 19%. However, the studies were too heterogeneous (I^2=97.6) to formally combine in a meta-analysis.

Figure 2.2 presents the infertility estimate and 95% confidence interval (CI) from each of the studies included in the analysis plotted chronologically (by when the study was conducted, not published).

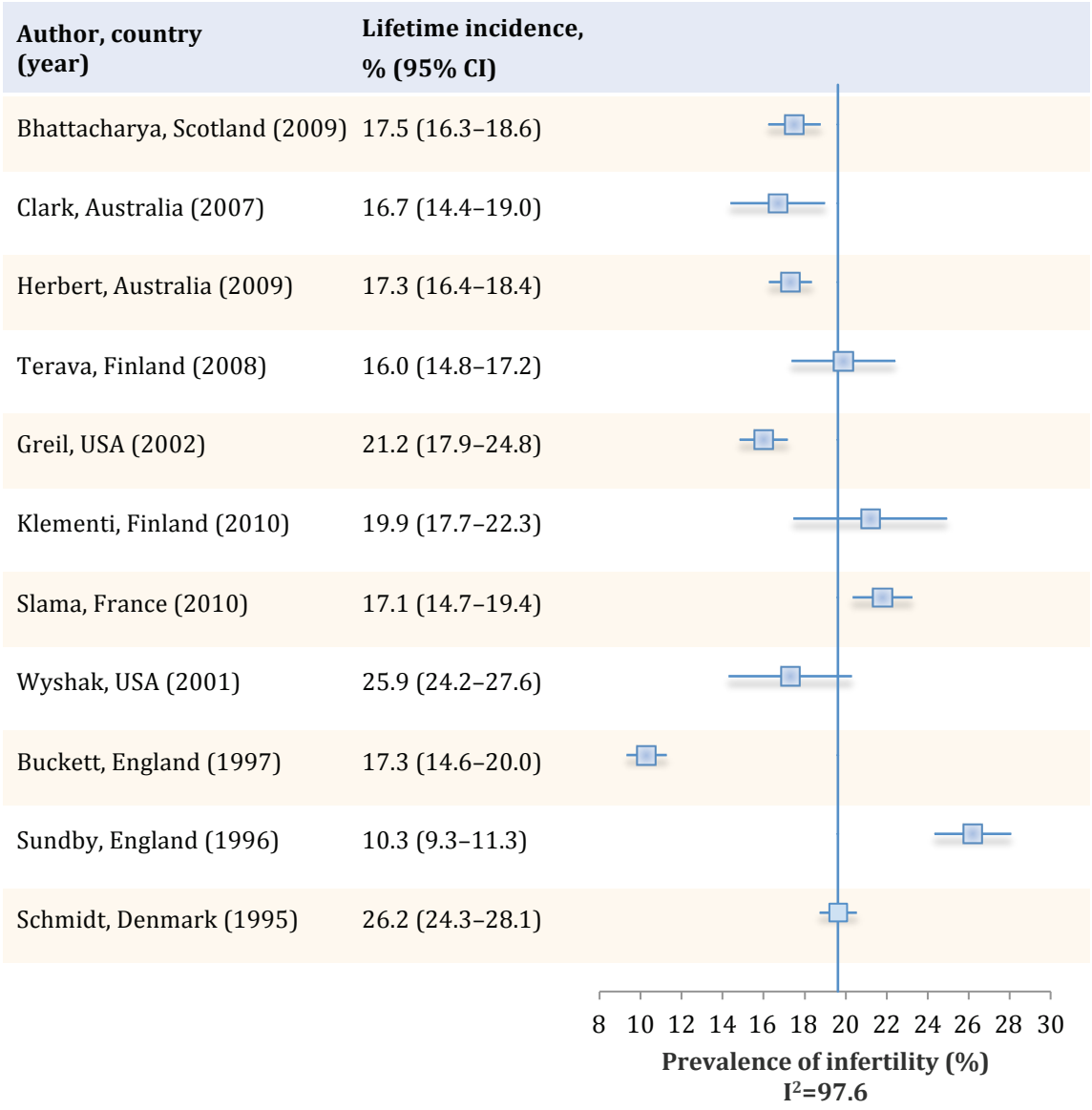


Figure 2.2: Forest Plot of studies in middle to high-income countries, measuring the lifetime cumulative incidence infertility (12 months or more trying to conceive) amongst studies that included women under 50 years old

Current prevalence of infertility

There were four studies examining current infertility in middle to high-income countries, all of which covered a similar age range of 15, 16 or 18 to 44 or 45 years.

Estimates of 12-month infertility ranged from 3.5–16.7% (refer to Table 2.1). Three studies in England measured primary unresolved infertility; this was 2.2% in 1993 (Gunnell and Ewings, 1994), 2.4% in 1995 (Buckett and Bentick, 1997), and 2.4% in 2001 (Oakley *et al.*, 2008). Involuntary childlessness, a useful measure, but not strictly an epidemiological or clinical measure of infertility (as women may have been pregnant but not had a live birth), was measured in five studies and was between 4.1% and 4.3% for all but one study (Rostad *et al.* [2006] measured this in Norway at 1.8% as mentioned previously) (Schmidt *et al.*, 1995, Buckett and Bentick, 1997, Oakley *et al.*, 2008, Klemetti *et al.*, 2010). Comparing the results from studies on involuntary childlessness and primary unresolved infertility reveals that just under half of women who were primarily involuntarily infecund (childless) experienced pregnancy.

Patterns of infertility

The changing definitions of infertility make it difficult to deduce any trends over time or differences between regions when comparing studies. Figure 2.2 shows studies of 12-month lifetime infertility plotted in chronological order; there is no trend over time visible. Some studies examined time trends within the study. Gunnell and Ewings (1994) found no evidence of changing prevalence by age cohort in their study in the United Kingdom (UK) in 1993. Templeton (1990 and 1991) also did not find evidence of changing levels of infertility in the early 1990s, but did see changes in service access for infertility.

The five studies examining current infertility were all in different countries and at different times and, therefore, no patterns could be inferred between studies. Stephen and Chandra (2006), however, found a statistically significant decline in 12-month infertility between 1982 and 2002 amongst married/cohabiting women in the USA.

In contrast to infertility in low-income countries, where it was measured, the levels of reported primary and secondary infertility in middle to high-income countries were approximately equal or there was a slightly higher level of primary than secondary infertility. This is not surprising given the generally increased age of

childbearing (leading more often to primary infertility) and improved birthing practices, abortion and reduced infections (which reduces the risk of secondary infertility) in middle to high-income countries.

2.6.2 Levels and patterns of infertility in low-income countries

Lifetime cumulative incidence of infertility

Twelve studies were reviewed for infertility estimates in low-income countries, but only three measured the lifetime cumulative incidence of infertility (refer to Table 2.2). These studies were in women across a wide age range, but generally amongst women who were still in the reproductive age range (15 or 19 years to 44 or 49 years of age). The studies were carried out from 1997 onwards, the most recent and largest being an Iranian study in 2004–5 with 10,783 participants (Vahidi *et al.*, 2009). The lifetime estimates of infertility for 12 months or more were 24.9% and 15.1% in Iran and India respectively (Zargar *et al.*, 1997, Vahidi *et al.*, 2009). Fuentes and Devoto (1994) measured the lifetime cumulative incidence of 12-month infertility at 25.7% in a smaller study in Chile amongst married women aged from 23–53 years.

Prevalence of current infertility

There have been two separate studies in Iran estimating infertility of 12 months or more at 3.4% (primary infertility only) and 3.4% (primary and secondary infertility; primary infertility in this study was 2.1%) (Ahmadi Asr Badr *et al.*, 2006, Vahidi *et al.*, 2009). Although another study estimated current infertility of two years or more in Iran at 8.0%, with primary infertility being 4.6% (Safarinejad, 2007). These studies all had large sample sizes with close to 100% response rates, were conducted within three years of each other (between 2002 and 2005) and were amongst married women in the reproductive age group. Why the two-year primary infertility estimate was higher than 12-month estimates is not immediately obvious. However, Safarinejad (2007) included all ever married women in his study, not just currently married women, which may have influenced their findings, given the desirability of children in this culture. If not being able to

have children increases the risk of divorce, then including women who have been married, but are not currently married, may increase the estimate of infertility.

The two studies from China both had relatively low estimates of infertility. One estimated infertility based to trying to conceive for two years or longer at 5.0% amongst women aged 18–49 years (Li *et al.*, 1990). This study was conducted in 1986. The other in 1988, amongst married women aged 15–57 years, measured primary infertility lasting for a much longer duration, seven or more years of unprotected intercourse, at 1.3% (Liu *et al.*, 2005). Neither of these studies discussed China's one child family planning policy in relation to primary versus secondary infertility levels, one study did not appear to differentiate primary and secondary infertility, and the other included only primary infertility. But, presumably, even after accounting for miscarriages and terminations, primary infertility would be predominant in China.

Geelhoed *et al.* (2002) measured current 12-month infertility in rural Ghana at 11.8% in 1999 and at a similar time Moshen *et al.* (2001) found the prevalence in rural Egypt to be 10.4%. Studies in Nigeria in 1991 and Gabon in 1986 had much higher estimates of current infertility of 30.3% and 25.4% respectively (Adetoro and Ebomoyi, 1991, Schrijvers *et al.*, 1991). All of these studies were based on a definition of non-contracepting (rather than 'trying') and amongst a wide age range of women from 15–54 years.

Two further studies, from Chile in 1990 and Thailand in 1981, had 12-month infertility measures of 7.0% and 13.4% respectively (Koetsawang *et al.*, 1985, Fuentes and Devoto, 1994). Both of these studies were in reproductive aged married women using the definition of unprotected intercourse.

Patterns of infertility

It was not possible to infer any trends over time due to the very different populations studied and the varying definitions used. However, an Iranian study reported increasing levels of primary infertility over time (by marriage cohort), rising from 2.6% in the 1985–89 cohort to 5.5% in the 1995–2000 cohort

(Safarinejad, 2007). However, age at first marriage was also increasing during this time, so could have confounded this observation.

Geographic variations in the prevalence of current infertility were evident, with women in the studies from sub-Saharan Africa suffering the highest levels of infertility, especially secondary infertility.

2.6.3 Summary: Patterns of infertility

Infertility was highly variable by country and difficult to compare due to the different definitions and no obvious trends over time were discernable. Recent studies in Western Europe, the USA and Australia yielded similar results for 12-month lifetime cumulative incidence of infertility of 17–22%. These studies were, however, in varying age groups and, despite being well-designed studies, the estimates may be subject to response bias as many of the studies had unsatisfactory response rates.

Studies in low-income countries had higher 12-month estimates (many were above 10% for the current prevalence of infertility), but they used the World Health Organization definition, so cannot easily be compared with the results of studies from middle to high-income countries. Iran and China were exceptions and had, relative to other low-income countries, lower levels of infertility. In many low-income countries secondary infertility was more commonly reported than primary infertility, this was not the case in middle to high-income countries.

Table 2.1: Population-based studies on levels of infertility and service use for infertility in middle to high-income countries

First author & year	Population			Survey methods			Participation		Levels of infertility		Service use by infertile	
	Study year	Country	Age grp (yrs)	Sampling, sample frame	Data collec-tion	Denominator for infertility	Sample size	Response rate %	Lifetime incidence %	Current prevalence %	Accessed service* %	Received treatment %
Infertility definition: Attempted to conceive for 12 months or longer												
Bhatta-charya 2009	2007	Scotland: North east	31-50	SRS from GP register	Postal form	Women who tried and/or conceived	4,066	50	17.5	-	73.6†, 67.1†	-
Clark 2007	2006	Australia	>= 18	Stratified sample using random digit dialling	CATI	All women	1,200	-	16.7	-	41.0	-
Herbert 2009	2006	Australia	28-33	Women in a cohort study (formed from SRS of national health insur-ance database)	Postal form	Women who tried and/or conceived	5,936	75	17.3	-	71.7	34.5‡
Terava 2008	2002	Finland	24-64	SRS from six regions in Finland (details of the list that the SRS was made from were not provided)	Postal form	All women	4,371	76	16.0	-	57.0	-
Greil 2004	2002	USA: upper Mid-west states	25-50	Random sample (details of the list that the sample was made from were not provided)	CATI	All women	580	63	21.2	-	54.5	25.0

Table 2.1 ***continued***

First author & year	Population			Survey methods			Participation		Levels of infertility		Service use by infertile	
	Study year	Country	Age grp (yrs)	Sampling, sample frame	Data collect-ion	Denominator for infertility	Sample size	Response rate %	Lifetime incidence %	Current prevalence %	Accessed service* %	Received treatment %
Herbert 2009	2001	Australia	53-58	Women in a cohort study (formed from a SRS of national health insurance database)	Postal form	All women	13,715	70	11.0¶	-	37.7	-
Klemetti 2010	2000	Finland	30-44	Cluster sampling of districts with SRS from sampled areas (details were not provided)	Inter-view	All women	1,198	87	19.9	-	56.1	-
Slama 2008 & Moreau 2010	2000	France: Brittany	18-60	SRS of telephone numbers within four towns	CATI	Women who tried and/or conceived	1,183	89	17.1	-	34.6§	-
Wyshak 2001	1996-97	USA	37-70	All living alumnae of 10 colleges	Postal form	Women who tried and/or conceived	3,293	85	25.9	-	78.4	-
Buckett 1997	1995	England: Shrop-shire	45-55	SRS from the primary care register	Postal form	All women	728	85	17.3	-	48.4	16.7
Rostad 2006	1985, 1995	Norway: North Trøndelag	50-69	All citizens of the county	Postal form	All women	9,983	86	4.8	-	-	-

Sundby 1996	1992-93	Norway: South Trøndelag	40-42	All citizens of the county	Self-completed form	All women	4,034	79	10.3	-	-	-
Van Balen 1997	1992	The Netherlands	25-49	SRS of all households	Interview	All women	3,295	-	10.7‖	-	65.6	-
Schmidt 1995	1989	Denmark: Copenhagen county	15-44	SRS (details of the sampling frame were not provided)	Postal form	Women who tried and/or conceived	2,865	78	26.2	-	47.4	-
Infertility definition: Attempted to conceive for 24 months or longer												
Bhattacharya 2009	2007	Scotland: North East	31-50	SRS from GP register	Postal form	Women who tried and/or conceived	4,066	50	9.1	-	-	-
Buckett 1997	1995	England: Shropshire	45-55	SRS from the primary care register	Postal form	All women	728	85	12.0	-	-	-
Templeton 1991	1988	Scotland	36-40	Random sample from GP register	Postal form	All women	1,064	86	14.7	-	89.2	-
Templeton 1990	1988	Scotland	46-50	Random sample from GP register	Postal form	All women	766	86	14.1	-	69.4	-
Infertility definition: Unprotected intercourse for 12 months or longer without conceiving												
Greil 2004	2002	USA: upper Mid-west states	25-50	Random sample (details of the sampling frame were not provided)	CATI	All women	580	63	33.8	-	39.3	-

Table 2.1 ***continued***

First author & year	Population			Survey methods			Participation		Levels of infertility		Service use by infertile	
	Study year	Country	Age grp (yrs)	Sampling, sample frame	Data collection	Denominator for infertility	Sample size	Response rate %	Lifetime incidence %	Current prevalence %	Accessed service* %	Received treatment %
Stephen 2006 & Chandra 2010	1982-2002	USA	15-44	Multistage probability samples of the household population	Interview	Married or cohabiting women	15,303	-	-	2002: 7.4 1982: 8.5	38.5**	9.0**
Philippov 1998	1998	Russia: Tomsk, Western Siberia	18-45	SRS from polling station lists	Interview	Married women	2,000	57	-	16.7	76.3	-
Rostad 2006	1985, 1995	Norway: North Trøndelag	50-69	All citizens of the county	Postal form	All women	9,983	86	6.6	-	-	-
Gunnell 1994	1993	England: Somerset	36-50	SRS from the Family Health Services register	Postal form	All women	2,377	76	26.4	-	44.8	-
Karmaus 1999 & Olsen 1996	1991-3	Denmark Germany Poland Italy Spain	25-44	SRS from population registers and electoral rolls available in each country	Interview	All women	6,630	70–87 varying by country	29.0††	-	49.0	-
Kuppers-Chinnow 1997	1991-2	Germany		SRS from population register	Interview	All women	1,531	-	31.8	-	54.9	-
Webb 1992	1988	Australia: Perth	16-44	Cluster sampling of census districts with random selection of starting point	Interview	Married women	1,495	90	22.8	3.5	48.9	-

Infertility definition: Primary unresolved infertility of 12 months of more												
Oakley 2008	2001	United Kingdom	40-55	SRS from electoral registers	Postal form	Women who tried and/or conceived	6,584	46	-	2.4	-	-
Buckett 1997	1995	England: Shrop-shire	45-55	SRS from the primary care register	Postal form	All women	728	85	-	2.2	-	-
Gunnell 1994	1993	England: Somerset	36-50	SRS from the Family Health Services population register	Postal form	All women	2,377	76	-	2.2	-	-
Sundby 1996	1992-93	Norway: South Trøndelag	40-42	All citizens of the county	Self-com-pleted form	All women	4,034	79	-	2.6	-	-

– *Not reported.*

* *Attended a general practitioner or specialist for problems conceiving.*

† *Definition also includes 'sought medical help', amongst women aged 36–40 and 46–50 respectively, no overall number for 'seeking medical advice' given.*

‡ *Included only hormonal treatment and/or IVF.*

§ *Amongst women who achieved a pregnancy following one year or more trying.*

¶ *Included women who had diagnosed infertility in their definition.*

|| *Measured primary infertility only.*

** *Ovulation drugs not included.*

†† *For the most recent period of unprotected intercourse only.*

SRS *Simple random sample.*

Table 2.2: Population-based studies on levels of infertility and service use for infertility in low-income countries

First author & year	Population			Survey methods			Participation		Levels of infertility		Service use by infertile	
	Study year	Country	Age grp (yrs)	Sampling, sample frame	Data collection	Denominator for infertility	Sample size	Response rate %	Lifetime incidence %	Current prevalence %	Accessed service %	Received treatment %
Infertility definition: Attempted to conceive for 12 months or longer												
Zargar 1997	1997	India: Kashmir	15-44	Cluster sampling with random sample of married women from selected villages (details of sampling frame not provided)	Inter-view	Women married ≥1 year	10,063	100	15.1	-	-	-
Infertility definition: Attempted to conceive for 24 months or longer												
Li 1990	1986	China: Jiangsu province	18-49	Stratified prob-ability sampling with random sample of married women (details of sampling frame not provided)	Inter-view	Married women	2,578	90	-	5.0	-	-
Infertility definition: Unprotected intercourse for 12 months or longer without conceiving												
Vahidi 2009	2004-5	Iran	19-49	Cluster sampling with random sample of households from a census list	Inter-view	Married women	11,381	95	24.9*	3.4*	-	-

Ahmadi Asr Badr 2006	2004	Iran: Tabriz	15-49	Random cluster sampling (no further details given)	Inter-view	Married women	2,623	93	-	3.4	-	-
Mohsen 2001	2001	Egypt: Kafr El Sheikh province	15-49	Systematic sample of family health records	Inter-view	Married women	1,125	97	-	10.4	-	-
Geelhoed 2002	1999	Ghana: Berekum District	15-49	Systematic sample of households	Inter-view	All women	1,073	98	-	11.8	-	-
Fuentes 1994	1990	Chile: down-town Santiago	23-53	SRS of newly married women from 1982 list matched to the electoral roll	Inter-view	Women married 8 years	474	89	25.7	7.0	27.0	-
Infertility definition: Unprotected intercourse for 18 months or longer without conceiving												
Adetoro 1991	1985	Nigeria: Shao village	15-49	Systematic sampling of all households in the village	Inter-view	All women	749	92	-	30.3	-	-
Infertility definition: Unprotected intercourse for 24 months or longer without conceiving												
Safarine-jad 2007	2002	Iran	15-50	Random cluster sampling of census units, with systematic selection from polling station list within each unit	Inter-view	Women married for ≥2 years	12,285	93	-	8.0	-	-

Table 2.2 ***continued***

First author & year	Population			Survey methods			Participation		Levels of infertility		Service use by infertile	
	Study year	Country	Age grp (yrs)	Sampling, sample frame	Data collection	Denominator for infertility	Sample size	Response rate %	Lifetime incidence %	Current prevalence %	Accessed service %	Received treatment %
Schrijvers 1991	1986	Gabon: Haut-Ogooue province	15-54	Random cluster sampling of villages with all residents of selected villages included	Inter-view	Menstruating women	716	-	-	26.6	-	-
Koetsaw-ang 1985	1981	Thailand: Bangkok and four rural areas	15-48	SRS of households from the district's Household Family Registers	Inter-view	Married women	1,516	-	-	13.4	-	-
Infertility definition: Unprotected intercourse for seven years or longer without conceiving												
Liu 2005	1988	China: Qinghai Province, Tibet and Xinjiang Regions	15-57	All married women in the regions	Inter-view	Married women	322,287	-	-	1.3*	-	-

– *Not reported.*

* *Measured primary infertility only.*

2.7 Results: Studies evaluating service use for infertility

The 30 studies reviewed for infertility service use and outcomes have been summarised in Tables 2.1–2.3. Tables 2.1 and 2.2 (on pages 37 and 42 in the previous section) include summaries of 21 studies that investigate service use for infertility in population-based studies in middle to high-income and low-income countries respectively. Table 2.3 on page 56 summarises the nine clinic-based studies (three of which were all on the same patient group). The studies in these tables are ordered chronologically according to the year the study was conducted, starting with the most recent study.

2.7.1 Patterns of service use for infertility in middle to high-income countries

Proportions seeking infertility services and patterns of referral

There were 20 population-based studies that measured the proportion of women with infertility that accessed services; this proportion ranged from 35–89% (see Table 2.1). These studies had varying definitions of infertility and varying definitions for accessing service, so cannot be compared over time or by region. Greil and McQuillan (2004) included data on service use for two infertility definitions: The first was trying to conceive and the second was unprotected intercourse for 12 months or more. They found that the proportions accessing services were 55% and 39% respectively. In general, the proportions accessing services were higher amongst those studies where the trying to conceive definition was used.

A few studies have looked at patterns of referral. In two population-based studies in England, just under two-thirds of women who sought assistance from GPs were referred to specialist hospital services (Gunnell and Ewings, 1994, Buckett and Bentick, 1997). Wilkes *et al.* (2009) found in their clinic-based study that three-quarters of infertile couples were referred to specialist help from GP practices in England. This study also notes that service seeking appeared to be higher amongst

older women with a shorter duration of infertility than in a survey done by Hull *et al*. in 1985. In 1983–4 Hull *et al.* (1985) found that women presented to specialist services with an average age of 28 years and average duration of infertility of 29 months. Over a similar time period a clinical study in Australia found similarly that women presented to services most frequently between the ages of 25 and 29 years with infertility generally lasting at least two years. The mean duration of infertility amongst women referred to tertiary services in New Zealand between 1998 and 2005 was 32 months and the average age at referral was 33 years (Gillett *et al.*, 2012). This trend towards older age at first presentation to clinical services correlates with a trend over time towards a voluntary delay in childbearing occurring in many middle to high-income countries.

Service seeking time trends

Amongst studies that looked at service use time trends, almost all the evidence supports an increase in service access over time; apart from a study by Chandra and Stephen (2010), which found a small, but statistically significant decrease in service use between 1995 and 2002 in the USA. In Scotland, both Templeton *et al.* (1990 and 1991) and Bhattacharya *et al.* (2009) found increasing levels of service access for the younger cohort when comparing those aged 36–40 years and those aged 46–50 years. An analysis of the trend within the age range of 36–50 years in England showed an increase both in GP consultation and of subsequent referral for specialist help in successively younger age cohorts of women for both primary and secondary infertility (Gunnell and Ewings, 1994). Data from France also reveal a trend towards greater proportions of women accessing services over time (Moreau *et al.*, 2010).

Predictors of service seeking

Amongst studies that looked at predictors of help-seeking behaviour there were common themes, with parity (being nulliparous), higher levels of education and being older predicting higher levels of service access (Schmidt *et al.*, 1995, Terava *et al.*, 2008). Chandra and Stephen (2010) also found that higher income predicted service seeking and that having treatment was predicted by older age and lower

parity. In England, occupational social class was also related to service seeking from GPs; the highest classes were more likely to access services. However, social class differences were not seen in referral to hospital services (Gunnell and Ewings, 1994). In an Australian study women were more likely to seek help if they had a history of endometriosis or PCOS. They were less likely to seek help if they had never been pregnant or if they had had terminations, if they were obese or if they were smokers (Herbert *et al.*, 2009b). This study's findings were slightly contradictory to other studies; however, as it was conducted in younger women (aged 28–33 years) the findings are probably not generalisable to women over the age of 35 years.

Causes of infertility

Infertility causes (the proximal risk determinants discussed in Section 1.4.1 on page 7) can be further grouped as male factor (usually sperm quality and/or quantity issues); female factor (most commonly ovulation disorders, endometriosis and other pelvic conditions including tubal disease and pelvic adhesions); or if both male and female infertility is present then it is referred to as combined factor and can include coital difficulties. Infertility may also be unexplained or undiagnosed. These causes of infertility have underlying intermediate and distal risk determinants as previously discussed in Section 1.4 (page 6). This review of population and clinical studies did not explore all of these risk determinants, however, the diagnoses/causes of infertility by country are discussed below.

United Kingdom: Amongst population-based surveys the most common self-reported causes of infertility in Scotland were ovulation disorders, sperm quality problems and unexplained; each of these diagnoses accounted for approximately 30% of infertility for women with a diagnosis (Bhattacharya *et al.*, 2009). In 1997 Bucket *et al.* (1997) reported that the most common diagnoses in a small study in England were no identified cause (29%), ovulatory (24%), male factor (14%) and tubal factor (14%). From the most recent clinical study in England, the most common causes of infertility amongst women with a diagnosis were ovulation disorder (25%), semen disorder (25%) and unexplained infertility (38%) (Wilkes

et al., 2009). In this study 64% of couples had a diagnosis one year after meeting the infertility definition at the GP and seven per cent of couples had more than one recorded diagnosis. In an earlier study in 1982–3 in England, the most common causes were very similar; ovulation disorder (21%), sperm disorder (24%) and unexplained infertility (28%) (Hull *et al.*, 1985).

Denmark: A study in 1995 found 42% of cases were due to sperm problems, 21% tubal damage and 20% ovulatory failure. Overall, in this population infertility causes were due to female factor alone in 36% of cases, male factor alone in 38% of cases and combined factor in 26% of cases (Schmidt *et al.*, 1995).

USA: In a survey of college alumnae, the most frequent causes were unexplained infertility (44%), sperm problems (21%), ovulation disorders (20%) and endometriosis (11%) (Wyshak, 2001). In another study amongst the general population, it was found that the most common causes were ovulation disorders (26%), male factor (22%), blocked tubes (17%), other tubal/pelvic problems (14%) and endometriosis (18%) (Stephen and Chandra, 2000). This study's participants had very high rates of tubal and pelvic causes compared with other studies, and infertility was attributed to STIs in 12% of cases. The differences in these two studies may have been due to study design and the questions used, or may be explained by differing social classes surveyed. In a separate 1983 clinic-based study, 40% of couples were found to have multiple factors contributing to their inability to conceive. In 33.3% two factors were present, and in 7.1% three or more factors were found; combined factor infertility was present in 20% of couples (Verkauf, 1983).

Australia: A 1976–89 clinical study of patients meeting the 12-month infertility definition reported that the major causes of infertility were semen defect (22%), irregular cycles or anovulation (29%), and pelvic disorder (a previous used grouping that included endometriosis) (57%); 16% of cases were unexplained. Trends over this time period displayed no change in semen defect diagnoses, but decreased ovulation disorders and increased pelvic disorders (due to increasing diagnoses of endometriosis) (Weiss *et al.*, 1992). Overall, 56% of infertility was attributed to female factor alone, 28% to male factor alone and 18% to combined

factor. Webb and Holman (1992) found in their 1988 survey that the risk of infertility increased with the number sexual partners, and the risk was greater in women with a history of PID or surgery for a ruptured appendix.

New Zealand: Data from the OFS collected from 1998–2005 showed that 43% of infertility was attributed to female factor alone, 26% to male factor alone, 16% to combined factor and a further 15% of infertility was unexplained (Gillett, 2007).

The difficulty with most of the diagnostic classifications used in these various studies was that each cause was treated as mutually exclusive, whereas in reality many women/couples have multiple factors. Further analysis of OFS data revealed that for women diagnosed with endometriosis 71% were diagnosed with at least one other factor (Gillett *et al.*, 2013). When considering treatments and/or outcomes, it would be useful to have further consideration of multiple diagnoses.

Treatment

From self-reported information from population-based studies, the overall proportion of infertile women receiving treatment varied considerably from 9–33%. But as mentioned, for self-reported treatment, there was almost no consistency in the definition of treatment. The few studies that gave details of the treatments provided to infertile women/couples are discussed below by country.

England: Wilkes *et al.* (2009) reported that half of those couples identified as infertile in their primary care-based study received treatment, the vast majority receiving this after referral to secondary and tertiary settings, and 10% of couples withdrew from investigation/treatment before a pregnancy occurred. The most common treatment was IVF/ICSI (51%) followed by ovulation induction (16%).

USA: In 1995 the most frequent services received by infertile women were advice (60%), diagnostic tests (50%), and drugs to induce ovulation (35%); fewer than 2% had used ART (Chandra and Stephen, 2010). Wyshak (2001) reported that amongst college alumnae treatment with clomiphene/clomid for OI was received by 40% of women, pergonal for OI by 19% and IVF by 11%.

Australia: Clinical data up to 1989 showed the most common treatments were ovulation induction (51%), IVF/gamete intra-fallopian transfer (42%) and donor insemination (18%) (Weiss *et al.*, 1992).

New Zealand: Data from the OFS showed that overall 66% of people attending specialist clinical services received treatment, with just over half of all clinic attenders receiving IVF (Gillett *et al.*, 2012). Data from another New Zealand clinic were also presented; trends towards increasing rates of treatment with IVF and improving success rates for IVF treatment were noted (Gillett, 2007).

Outcomes after infertility

Very few population-based studies reported on pregnancies and/or live births in the context of having received treatment (or not). In Buckett and Bentick's (1997) study in England in 1995 they found little difference in conception rates for those who were treated and those who were not treated for infertility (71% and 75% respectively. Bhattacharya *et al.* (2009) also found in Scotland little difference in the rates of conception for women with treated and untreated primary infertility (59% and 56% respectively). However, for secondary infertility those who received treatment had a much lower conception rate: 57% versus 95% in those who did not have treatment. One explanation for this could be that spontaneous pregnancies and treatment related pregnancies are competing risks (they are mutually exclusive events; a treatment related pregnancy cannot occur if a spontaneous pregnancy has already occurred). Therefore, those women who did not have treatment may have conceived before it was possible for treatment to begin (and if they had had treatment it would more than likely have been successful). However, unless treatment provision time periods were considerably shorter for women with primary infertility, then this difference should also have arisen in women with primary infertility. It should also be noted that women from studies conducted in the 1990s (and also more recent studies that include older women) would have received treatment before the widespread uptake of IVF.

Further to the difference in conception rates, Bhattacharya *et al*. (2009) also found in their study that the self-reported proportion of pregnancies ending in a live

birth was significantly lower for women with secondary infertility compared with those with primary infertility or no infertility. One limitation of this study is that whether or not the pregnancies following treatment actually resulted from treatment could not be determined.

Templeton *et al.* (1991) found that women with infertility were more likely to have a spontaneous abortion that those with no fertility problems. In this study they also found no difference in conception rates for women who did or did not consult a doctor, but no information on treatment was available. Wyshak (2001) found that in college alumnae in the USA, 45% of infertile women who sought treatment had a successful outcome, however *successful outcome* was not further defined as either a conception or live birth and no information was given on the success rates for those who did not have treatment. Schmidt *et al.* (1995) reported that in their 1989 study in Denmark, 55% of women treated for infertility had subsequently had a child. Among these women who had a child, 33% reported that the successful pregnancy was treatment-related and 55% that the child was spontaneously conceived; the remaining women had a new partner, had adopted or did not know whether their pregnancy was treatment-related. The study reports that overall half of women who experienced infertility had a spontaneous live birth.

In the most recently published clinical study, Wilkes *et al.* (2009) reported that one year following being diagnosed with fertility problems by a GP, 10% of women had a spontaneous conception and 26% had conceived following treatment. This is low compared with population-based studies where rates of conception with or without treatment are above 50%, but this could be explained by the time limit of one year of follow up after being diagnosed infertile. Earlier, Hull *et al.* (1985) did not show any overall results for those who were treated or not treated, instead focussing on conception rates by infertility cause. Those with ovulation disorders reached near normal cumulative conception rates of about 95% after two years, those with unexplained infertility had conception rates of around two-thirds that of normal, but those with sperm dysfunction had very poor conception rates (10% after two years). Clinical data from 1983 in the USA shows cumulative conception

rates for treated infertility patients as being 60% after five years of follow up, with no significant differences by category of diagnosis (single factor, multiple factor or unexplained infertility) (Verkauf, 1983).

New Zealand data from the OFS showed that of women who did not withdraw from the clinic, 31% had a spontaneous pregnancy resulting in live birth, 50% following treatment, and the remaining 19% had either completed and failed treatment or opted not be treated (Gillett, 2007). The data also suggest that women with unexplained infertility have the highest rates of spontaneous conception, whereas treatment success was highest for women with anovulation. This study may have underestimated the percentage of women who conceive spontaneously due to the lack of data on women who withdrew from the service, and also those that fail treatment may still spontaneously conceive after losing contact with the service. Gillett *et al.* (2006) also reported in a previous study on the same group of patients that treatment success (having a live birth) was lower amongst women who were obese (a BMI of 32kg/m^2 or more), although it appeared that there was no relationship between spontaneous conception and BMI amongst infertile women.

2.7.2 Patterns of service use for infertility in low-income countries

Service seeking

Fuentes and Devoto (1994) found that 27% of women with infertility for 12 months or longer (by the definition of unprotected intercourse) consulted a physician in Chile. Interestingly, the majority (62%) of infertile women did not consider their infertility to be a medical problem. There were no other population-based studies in low-income countries. A Sri Lankan clinic-based study conducted from 1976–1988 reported that the mean age of presentation for women to a clinic was 28.8 years (Gunaratne and Seneviratne, 1992). The mean age of presentation found by Bayasgalan *et al.* (2004) in Mongolia was similar at 29.7 years (data from 1998-2002). In Mongolia, the majority (83.5%) of women had infertility for longer than two years before consulting the infertility service.

Causes of infertility

Gunaratne and Seneviratne (1992) reported in Sri Lanka that 46% of infertility was due to female factor, 26% due to male factor and combined factor in 7%. Ovulatory disorders were the most common cause in females (31%), followed by tubal factor (27%). In Mongolia 46% of infertility was due to a female factor, 26% due to male factor, 19% combined factor and 10% of cases had no cause detected (Bayasgalan *et al.*, 2004). Tubal factor was the most common cause of infertility in women (33%), followed by ovulatory disorders (22%). A history of STI and PID was also common amongst those with female factor infertility and was significantly associated with secondary rather than primary infertility.

Treatment

No data on treatment were presented by the three studies reviewed.

Outcomes after infertility

No data on outcomes following infertility were presented by the studies in Chile and Mongolia. Clinical data from Sri Lanka showed that 14.5% of women presenting to the clinic had spontaneous pregnancies without treatment and 39.2% of women conceived after treatment (Gunaratne and Seneviratne, 1992). The proportion of women who had successful pregnancies was not mentioned.

2.7.3 Summary: Service use for infertility

Middle to high-income countries

There is a wide variation in the proportion of infertile women accessing services in middle to high-income countries, ranging from 35–89%. Amongst infertile women, the proportion who received treatment ranged from 9–33%. These studies were amongst women with varying timeframes for their infertility diagnosis (12 months and 24 months) and varying definitions (unprotected intercourse for 12 or 24 months and trying to conceive for 12 or 24 months); these variations make these data difficult to compare. Further to this, the definitions of accessing service and treatment were inconsistent or not specified adequately. It is likely that some of

the variation in treatment would be explained by the differing time frames of these studies and the country-specific policies regarding access to and funding for receiving ARTs. However, this could not be further analysed given the inconsistency in treatment definitions and paucity of epidemiological studies investigating treatment.

Most studies using the definition of 12 months trying to conceive have recorded access to service at around or over 50%. Data suggest that women are accessing infertility services in greater proportions over time and, according to studies that cover a wide range of ages, women are accessing services at older ages (due to delayed childbearing). Clinical data provided evidence that women are commonly accessing services when aged in their late twenties and early thirties. Being likely to access services is also most commonly predicted by low parity, high levels of education and high SES.

Amongst those who accessed services and had a diagnosis, the most common causes were usually ovulation and sperm disorders, with tubal factor infertility being less important. Although, in contrast, one study in the USA and another older study from Australia had higher levels of tubal factor infertility and reported associations with STIs. In most of these studies, between a third and one-half of infertility was due to female factor, a quarter to a third due to male factor and up to a quarter due to combined factor infertility. In general, comparing the earlier and more recent studies it appears that there has been a trend toward a decrease in the proportion of infertility attributed to female factor and slight increases in male factor and combined factor infertility.

Data from most studies (where it was available) suggest that for women with infertility, over 50% will either spontaneously conceive or conceive with treatment. Success rates appear to be either similar or slightly lower for women that receive treatment. This probably reflects a more severe form of infertility in women who receive treatment, rather than reflecting on the benefit of having treatment, although this level of detail was not given in any of the studies.

Low-income countries

Very little data were available that looked at service use for infertility (rather than infecundity) in low-income countries. In Chile, 27% of infertile women had consulted a doctor for infertility. This appears low, but the definition for infertility was based on 12 months of unprotected intercourse rather than actually trying, and the authors note that the majority of women who were infertile did not consider themselves to have a medical issue. Clinic-based studies in Sri Lanka and Mongolia revealed that women presented for services usually in their late twenties and had had infertility for at least two years.

In both clinical studies, almost half of infertility in couples was due to female factor and another quarter due to male factor, the rest being combined factor or no detectable cause(s). In Sri Lanka ovulatory disorders were the most common cause of infertility in females, followed closely by tubal factor. This was reversed in Mongolia and additionally they found a history of PID and STIs to be common amongst infertile women.

There were no data on treatment and the only data on outcomes for infertile women comes from the study in Sri Lanka where 14.5% of women had a spontaneous conception and 39.2% conceived following treatment.

Table 2.3: Clinic-based studies on service use for infertility

First Author & year	Population			Methods			Results – proportion of infertility attributable to:			Results –treatment and outcome		
	Study year	Location	Age grp	Study design	Data collection	Sample size	Female factor %	Male factor %	Combined factor %	Attenders treated %	Child from treatment %	Child not from treat-ment %
Middle to high-income countries												
Wilkes 2009	2005–6	England	15-44	Retrospective study of GP records on patients diagnosed with infertility	GP records	534	-	-	-	50.2*	9†	27†
Gillett 2006 & 2007 & 2012	1998–2005	New Zealand	-	Retrospective study of infertility clinic records on patients referred with infertility	Clinic records	1386	43	26	16	66	52	39
Weiss 1992	1976–1989	Australia	-	Retrospective study of infertility clinic records on patients referred with infertility	Clinic records	2895	56	10	18	-	-	-
Hull 1985	1982–3	England	-	Retrospective study of infertility clinic records on patients diagnosed with infertility	Clinic records	708	-	-	-	-	-	-
Verkauf 1983	1976–1980	USA	21-37	Retrospective study of private practice infertility clinic records	Clinic records	141	-	-	20	-	48.2	-

Low-income countries												
Bayasgalan, 2004	1998–2002	Mongolia	18-41	Prospective study of couple attending an infertility clinic	Clinical assessment	430	46	26	19	-	-	-
Gunaratne, 1992	1976–1988	Sri Lanka	-	Retrospective study of infertility clinic records	Clinical records	2002	46	26	7	-	39.2	14.5

– *Not reported.*

* *Treated with IVF or ICSI or ovulation drugs.*

† *Pregnancy measure up to one year after infertility for 12 months or longer was diagnosed.*

2.8 Results: Studies evaluating fertility knowledge and attitudes

Table 2.4 on page 62 summarises the 12 studies on knowledge and attitudes, 11 in middle to high-income countries and one in a low-income country. The studies in this Table are also ordered chronologically according to the year the study was conducted, starting with the most recent study.

2.8.1 Findings for knowledge and attitudes

Middle to high-income countries

Overall, knowledge about fertility/infertility was poor. In a Canadian survey of childless women, the majority of participants rated themselves as having some knowledge or being fairly knowledgeable about fertility, but on questions assessing their fertility knowledge 50% of women answered less than 40% of the questions correctly (Daniluk *et al.*, 2012).

The same study found that most women were aware of the age-related fertility decline in women (Daniluk *et al.*, 2012), as did a Canadian study of high school students (Quach and Librach, 2008). However, other studies found poor knowledge. In Finland, half of male university students and a third of female students thought fertility declined after 45 years; these knowledge levels were lowest amongst the youngest responders. Almost half of respondents over-estimated the chances of conception in a year amongst 35–40 year old women and over a third over-estimated for 25-30 year olds (Virtala *et al.*, 2011).

In Italian students, whilst they were aware of declining fertility with age, the age at which female fertility sharply declines was considered to be 45–55 years by 53% of females and 37% of males. The likelihood of conception was again over-estimated, with most students estimating this to be between 50 to 100% in one month (Rovei *et al.*, 2010).

Similarly, Swedish university students had overly optimistic perceptions of women's chances of becoming pregnant. About half of women intended to have

children after age 35 years and were not aware of the age-related decline of female fertility at this age (Lampic *et al.*, 2006).

When Ivy League students in the USA were asked until what age women are fertile, the average response was 46.1 years among female respondents. Furthermore, when asked when a woman is most fertile during her menstrual cycle, only a quarter of respondents were able to correctly identify the time period (Kuang *et al.*, 2006). So further to the lack of appreciating the age-related fertility decline and overestimating the likelihood of conception, it appears that even well educated men and women do not know when a woman is able to conceive (the fertile window).

One further survey in New Zealand that investigated this reported that even amongst women seeking clinical infertility services, attenders were unable to identify the fertile window (Blake *et al.*, 1997). Amongst these women, all of whom had been attempting to conceive for at least two years, only 15% were trying to time intercourse for the fertile window.

In an Australian survey, only 38% of women and 21% of men thought the woman's age was relevant in deciding when to have children, and only 9% of women expressed concern about fertility preservation. Despite 95% of women in this study agreeing that fertility declined with age, almost half of childless women aged 40–49 years thought they would be able to conceive whenever they wanted to (Clark and Mackenzie, 2007).

Three surveys, two in Canada and one in Wales, reported that respondents had reasonable knowledge of other recognised fertility risks such as STIs, smoking and being overweight (Bunting and Boivin, 2008, Vause *et al.*, 2009, Daniluk *et al.*, 2012). But, in Daniuk *et al.*'s (2012) study many participants falsely believed that health and fitness were more important than age, and that the birth control pill negatively influences fertility. Bunting and Boivin (2008) also found that both male and female university students were likely to believe in the positive effects of health habits. In Australia, only four per cent of women believed their partner's fertility could effect their chance of conceiving and no respondents thought a

man's age was a factor in requiring infertility treatment (Clark and Mackenzie, 2007); Daniluk *et al.* (2012) reported also there was an under-appreciation of the male contribution to infertility.

Regarding service use, in the Australian study 90% of women and 86% of men stated they would see a doctor if they had trouble conceiving. However, in the same study, of those with fertility problems, only 41% had consulted a doctor about them (Clark and Mackenzie, 2007).

In general, in most of the studies reviewed, whilst there was good awareness of ART and IVF, few survey respondents could correctly estimate the treatment success rates, with respondents both under and over-estimating the likelihood of treatment success (Lampic *et al.*, 2006, Clark and Mackenzie, 2007, Rovei *et al.*, 2010). Adashi *et al.* (2000) reported that overall there was a lack of knowledge about the definition of infertility (despite most respondents claiming to know someone affected by infertility) and that just 38% of people considered infertility to be a disease.

Overall, knowledge was poor in most of the studies reviewed, however, a general improvement was seen with higher education levels and better SES (Bunting and Boivin, 2008, Quach and Librach, 2008, Vause *et al.*, 2009).

Low-income countries

In the Pakistani survey just 46% of participants knew about the fertile period in women's cycles and over 50% of participants mistakenly believed that the use of intra-uterine devices and oral contraceptives could cause infertility. Lower levels of education were associated with fertility myths such as beliefs in evil forces and supernatural powers. Given this, alternative treatments for infertility were found to be very popular. Over three-quarters of participants were unfamiliar with IVF and most found this to be an unacceptable treatment option (Ali *et al.*, 2011).

2.8.2 Summary: Fertility knowledge and attitudes

Directly comparing studies on fertility knowledge and attitudes is not possible as there have been few studies amongst varying populations, all using a variety of questions and questioning styles.

Whilst most people in the studies reviewed appeared to be familiar with the term infertility and were familiar with some of its main risk factors, there was a general lack of knowledge in the population. Both men and women acknowledge that fertility declines with age. But, despite this knowledge, most people overestimated both the age at which fertility starts to decline and the likelihood of conception, even to the extent of expecting to be able to conceive 'on demand' when the female partner is over 40 years old. There appeared to be a lack of awareness of infertility due to male factor(s) and that male aging also plays a role in infertility. Whilst treatment options such as IVF were familiar, few people knew the likelihood of success with these treatments. In what seemed to be a contradiction, evidence from two studies suggested that the majority of people do not consider infertility to be a disease, yet at the same time, if faced with the inability to conceive in the future, the majority of people would seek medical help. However, in reality a far smaller proportion of infertile couples actually seek medical help that those who state they would in the future.

These studies have nearly all been in tertiary-educated people or in those attending clinics for infertility services. As higher education and SES are related to improved knowledge, and given that you would expect highly motivated clinic attenders to have reasonable infertility knowledge, overall these studies probably over-estimate the levels of knowledge in the general population. There is a lack of information about infertility perceptions and knowledge in the general population with only three studies in middle to high-income countries available, one of which did not have random sample and the other two providing information from only a few questionnaire items.

Table 2.4: Studies on fertility knowledge and attitudes

First Author & year	Population			Methods		Participation		Results
	Study year	Location	Age grp	Study design	Data collection	Sample size	Response rate (%)	Outcomes measured
Middle to high-income countries								
Daniluk 2012	2010	Canada	20-50	Survey of a population-based sample and a volunteer sample of childless women	Online form	3,345	N/A	Fertility knowledge and self-rated knowledge
Virtala 2011	2008	Finland	<35	National survey of male and female undergraduate university students	Online & postal form	5,086	51	Age-related fertility decline and likelihood of conception after one year of intercourse
Vause 2009	2008-9	Canada	-	Clinic-based survey of women presenting for initial consultation at an infertility service	Self-completed form	400	-	Knowledge of pre-conception fertility risks
Rovei 2010	2006-7	Italy	19-37	Survey of university students	Self-completed form	958	-	Fertility awareness and knowledge about Italian legislation on ART
Quach 2008	2006	Canada	-	Survey male and female high school students	Self-completed form	772	17[a]	Knowledge of fertility risks and attitudes towards fertility
Bunting 2008	-	Wales	-	Online survey of male and female university students and junior staff	Online form	149	-	Knowledge scores on fertility risk factors, myths and health habits
Clark 2007	2006	Australia	>= 18	National population-based survey of men and women	CATI	2400	-	Knowledge of age-related fertility decline, attitude towards delaying fertility and seeking medical assistance

Lampic 2006	2004	Sweden	-	Survey of male and female undergraduate university students	Postal form	401	67	Awareness of age-related fertility, chances of conception and IVF success rates
Kuang 2006	-	USA	-	Survey of male and female Ivy League college undergraduate students	-	390	-	Knowledge and opinions on reproductive potential
Adashi 2000	1998 -99	Belgium, France, Germany, Italy, Sweden, UK, USA, Australia	>= 15	Population-based survey of men and women	Telephone interview	8,194	-	Knowledge of and attitudes towards infertility
Blake 1997	-	New Zealand	-	Clinic-based survey of women attending a tertiary infertility service	-	80	-	Knowledge of the fertility window
Low-income countries								
Ali 2011		Pakistan	18-75	Survey of adults accompanying patients at tertiary care hospitals	Interview	447	97	Knowledge of and attitudes towards infertility

– *Not reported.*

* *The proportion of contacted schools that agreed to participate, no information on individual student participation.*

2.9 Summary: The population experience of infertility, infertility service access, and knowledge and attitudes towards infertility

The results from studies of the current prevalence and/or lifetime cumulative incidence of infertility are highly variable. The most recent studies in middle to high-income countries give a range for the 12-month lifetime cumulative incidence of 17–22%. Most studies in low-income countries generally have had higher 12-month estimates. Commonly, increasing age was a risk factor for infertility, but this was more of an influence in middle to high-income countries. Whilst the age of childbearing is increasing in these countries, it does appear that people are aware that this may impact on fertility, as generally there was reasonable general knowledge regarding age-related fertility. However, this did not translate to a good knowledge of the likelihood of conception; there were overly optimistic views on the likelihood of conception for all maternal ages, with beliefs that good fertility extended well into the mid-forties for women. There were also knowledge gaps regarding when women are fertile during their menstrual cycle, factors that influence fertility, and the impact of the male partner on infertility.

The proportion of infertile women accessing infertility help/services ranged from 37–89%. Some of the low levels of reported access may not entirely be due to gaps in service provision; it may also be in part due to knowledge of and attitudes toward infertility. Many women with infertility do not classify their infertility as a medical problem, and women classified as infertile due to having unprotected intercourse (rather than trying) may not actually want a pregnancy. Also, fear of discovering that there is a problem or not having positive treatment beliefs may be a barrier to woman accessing infertility services.

Clinical data from low-income countries suggest women first present to services in their late twenties after a duration of infertility of at least two years. This is similar to historic clinical data in middle to high-income countries, but more recent data from these countries suggest women are presenting at older ages and with shorter durations of infertility. Following similar patterns in both low-income countries and the older middle to high-income country data, more commonly female factor

infertility was found as a sole cause, with smaller proportions of male factor and combined factor. This is in unison with higher levels of tubal factor infertility and some association with STIs. More recent data in middle to high-income countries suggest a greater proportion of diagnoses being due to male factor and combined factor infertility. Recent studies from middle to high-income countries also suggest for women with infertility around half will spontaneously conceive and a slightly lower proportion of those who receive treatment will also conceive. The proportion of infertile women who receive treatment ranges from 9–33%. Treatment success rates were very poor in the early 1980s, but have improved over time. An increasing proportion of the treatments being ARTs, such as IVF, have accompanied these improved success rates.

Overall, in middle to high-income countries, despite 1) the increasing age of first childbirth, 2) rising concern over the effect of this trend on infertility, 3) a resulting increase in service use and 4) poor fertility knowledge in the population, figures on primary unresolved infertility and involuntary childlessness remain stable and relatively low. However, use of these figures may mask possible emotional and financial burdens associated with any increasing time spent trying to conceive a pregnancy, while also not taking into account desired family size, which may not have been attained.

2.10 Generalisability of the literature to New Zealand

In Australia and New Zealand, the only population-based studies measuring infertility levels were in Australia, where there have been four studies: Two were in narrow age ranges from the same on-going birth cohort and two other population-based surveys. Results from these studies are similar to recent studies in the UK and USA and could be relatively generalisable to New Zealand. However, New Zealand has proportionally a much larger indigenous population than Australia; Māori (and Pacific peoples) tend to have different fertility patterns to European New Zealanders and probably more STIs, both of which could effect overall patterns of infertility.

There is very little information available regarding access to infertility services from Australia, with three of the above studies reporting between 38% and 72% service access, but little further information, and no population-based studies from New Zealand that address patterns of service use. There were two clinical studies in Australia and New Zealand; data available on diagnoses and treatment outcomes from these studies fitted patterns seen in other middle to high-income countries.

Data from Australia suggest general knowledge regarding fertility is similar to other middle to high-income countries; whilst there is some awareness, application of knowledge to actual fertility outcomes is very poor. Whilst knowledge in New Zealand may be expected to follow a similar pattern, there are almost no data to verify this, with one small clinic-based study in Auckland that only addressed knowledge of the fertile time period within the menstrual cycle.

Overall, there is a paucity of infertility data from New Zealand. The results of studies from other countries may not be generalisable to New Zealand women and only a few clinical studies having been conducted in the New Zealand population. Due to the importance of infertility and the profound fertility changes over the past few decades, further research into infertility in New Zealand is needed.

2.11 Overall objectives of this thesis

Following consideration of the background regarding infertility issues and previous research findings, specific knowledge gaps were identified and used to formulate the objectives for this thesis. The overall objectives were to better understand infertility in the New Zealand context and make comparisons to infertility in other countries.

To achieve the main objectives three studies were undertaken in addition to the literature review: A population-based survey of infertility in Otago and Southland; a comprehensive analysis of Otago and Southland clinic-based infertility data; and a review of routine hospitalisation data on conditions related to infertility. These three studies were used to fulfil the following specific aims of this thesis:

1) To assess in women aged 25–50 years in Otago and Southland:
   - The experience of infertility.
   - The use (and outcome) of services by infertile women.
   - Variation of infertility prevalence and service use by demographic characteristics.
   - Knowledge amongst women of infertility and the effectiveness of treatments.

2) To investigate infertility service provision, causes of infertility and fertility outcomes amongst women attending secondary or tertiary care for infertility in Otago and Southland (both overall and by selected demographic characteristics).

3) To determine the feasibility of using national hospital discharge data to examine the rates and trends in infertility and markers of tubal factor infertility, and compare those data from Otago and Southland to the national figures.

CHAPTER THREE:

STUDY ONE: A SURVEY OF INFERTILITY IN OTAGO AND SOUTHLAND

Chapter Three outlines Study One: A population-based cross-sectional study of infertility, service use and knowledge amongst women resident in Otago and Southland. This chapter includes objectives, methods and results. The literature review regarding population based estimates of the prevalence of infertility, service use, treatment and outcomes for infertility was detailed in the previous chapter.

3.1 Background

Limited information is available on the number of women that experience infertility in New Zealand, their use of health services, and women's knowledge and attitudes about infertility and its treatment.

A cross-sectional study was undertaken in Otago and Southland regions of women aged 25–50 years to ascertain their reproductive history, their experience of infertility, whether medical help was sought and provided for infertility and the outcome. The study also analysed what factors might have contributed to infertility, and knowledge of fertility expectation by age, common causes of infertility and likely success of treatment.

The age range was specifically chosen to capture attitudes and knowledge from women who both have and have not experienced infertility. It also enabled data to be captured on women who had completed their fertility experience. Data from relatively older women in the sample will also be more directly comparable with women in the OFS clinical dataset (as it only includes new referrals up to the end of 2005); the OFS being the sole provider of tertiary infertility services in the Otago and Southland regions.

3.2 Study objectives

The collection and analysis of these survey data addresses the first overall aim for this thesis, which was:

To assess in women aged 25–50 years in Otago and Southland:

- Their experience of infertility.
- The use (and outcome) of services by infertile women.
- Variation of infertility prevalence and service use by demographic characteristics.
- Knowledge amongst women of infertility and the effectiveness of treatments.

3.3 Methods

3.3.1 Study design

A cross-sectional study design was chosen to estimate prevalence and due to the efficiency (in terms of sample size, duration and expense) of this design. The study was limited to residents of Otago and Southland, as this would allow for more robust comparison with the OFS dataset. The specific inclusion criteria were:

- On the electoral roll.
- Female.
- Resident in the Otago or Southland region on 14 December 2010.
- Aged 25–50 years on 14 December 2010.
- Adequate English language and intellectual capability to complete the questionnaire.

3.3.2 Consultation with Māori and ethical approval

Formal consultation with Māori though the University of Otago Ngāi Tahu Consultation Committee was undertaken and their approval was given.

Ethical approval was granted by the Southern Regional Ethics Committee in November 2010. As this was an observational study with minimal likelihood of harm, informed consent was considered to have been given if participants chose to complete the study questionnaire. As some of the survey questions were of a sensitive nature, with the potential to cause distress, women were given contact details for the principal investigator (who could urgently contact a clinician if required) at the start of the questionnaire. There were clear instructions to skip any questions that they did not feel comfortable answering. The telephone interviewers were highly trained and experienced in delivering sexual and reproductive health questionnaires.

3.3.3 Sampling Frame

The New Zealand electoral roll, a national registry of registered voters, was chosen as the sampling frame due to the relatively high population coverage and accessibility of this roll for research purposes. The electoral roll is compiled during general and provincial election years, and includes the names, ages, addresses and occupations of individuals from each electoral district who were registered to vote. By law, all persons who are eligible to vote are required to register on the electoral roll, even if they do not intend to do so. However, comparison between the 2006 New Zealand census and the electoral roll suggests that 10% of those eligible to vote are not registered on the electoral roll, with this being the case for 25% of people aged 18–30. This may impact on the representativeness of the women aged 25–30 years old within the study, if women who are enrolled differ significantly from those who are not, particularly in their fertility histories. Other issues to consider when using the electoral roll include differential coverage of the electoral roll (there are smaller proportions of people enrolled in some population sub-groups) and that, due to the high mobility of the New Zealand population, coverage of the electoral roll can decline significantly between elections (Electoral Commission, 2010). However, more significant limitations apply to the alternative more commonly used sampling frame option, telephone listings. Using telephone listings can now cause severe under coverage of the population due to the high

proportion of people without landline telephone numbers (Statistics New Zealand, 2003).

Electronic copies of the General and Māori electoral rolls were obtained from the Electoral Commission for local authorities in the Otago and Southland regions. The list was supplied with age (in single years, not grouped), limited to those aged 25–50 years of age on 14 December 2010. Because there is no gender indication, both men and women were included. There were 97,559 individuals in the list provided.

To minimise the likelihood of men being selected, individuals were excluded if their title was 'Mr' (n=42,301), 'Father' (n=4) or 'Master' (n=13). There were 8,819 individuals who did not have a title and 971 who had titles that were not gender specific (e.g. 'Dr', 'Professor', 'Rev'). Individuals without a title or a non-gender specific title were then excluded if they had a male specific first name. An internet search was conducted to identify a list of popular male names in the 1960s and 1970s. A visual inspection of the sample identified further names to exclude. Individuals with non-gender specific names such as 'Leslie' were only excluded if there were male specific middle names for that individual. The total number of individuals in the final sampling frame was 50,661.

3.3.4 Sample size calculation

A randomly selected sample of 2,000 women across the region and a response rate of at least 70% were required to achieve reasonably precise estimates; a sample of 1,400 would give an estimate of infertility to plus or minus two per cent and a 70% response rate would minimise selection bias due to non-responders. As there may have been males in the sampling frame and the electoral roll is considered to be 98.5% accurate, a sample of 2,200 was drawn from the electoral roll in order to ensure at least 2,000 women were selected.

3.3.5 Random sampling

A random number was generated for the 50,661 individuals in the sampling frame and the electoral roll was sorted by this number and the first 2,200 individuals

selected for the main study. To obtain a sample for piloting the recruitment process and questionnaire prior to the main survey, individuals were selected sequentially from the end of the sorted electoral roll and located in the white pages telephone directory. The first 30 individuals that had a telephone listing were included in the pilot.

3.3.6 Piloting

In May and June 2011 a pre-pilot survey was initially sent to six women who volunteered through Fertility New Zealand (these women were from various locations throughout New Zealand). The survey was also reviewed by colleagues and friends, and their feedback was obtained. The pre-pilot sample included two women who were in same sex relationships, and three women of Māori ethnicity who were identified for pre-piloting the questionnaire by colleagues in the Ngāi Tahu Research Unit. The Pacific Trust Otago was contacted to include Pacific women in piloting, but no response was obtained.

Following this preliminary pilot, the full process from initiating contact through to completing the survey was piloted on those 30 women who had been randomly selected for piloting. They were sent the invitation letter, reminder letter and given a telephone call if needed (described further in Section 3.3.8). Additionally, they were also sent a feedback form and prepaid return envelope. A $20 voucher was offered to pilot participants on completion of both the questionnaire and feedback form. Twenty-two of these 30 (73.3%) women completed the questionnaire.

The true piloting of this questionnaire amongst the general population allowed refining the process of enrolment, operation of the internet-based questionnaire and the telephone interviewing procedure (the platform/delivery of the questionnaire is described further in the next section). It also allowed for the completion time for the questionnaire to be more accurately gauged. Based upon feedback from both the preliminary piloting and piloting amongst the population, the following minor questionnaire alterations were made:

- The religion question was removed after two women strongly objected in their feedback forms and others did not answer the question.

- Questions were added on ovulation monitoring and intercourse timing behaviours after two women both suggested this would be interesting/useful.
- Clarified that *12 months unprotected intercourse* (used in the definition of infertility), was for heterosexual intercourse.
- The option 'Before I started trying' was added to the possible answers to the question on time spent trying before seeking treatment.
- Clarified the question on criteria for IVF eligibility, regarding BMI, the text was changed from 'BMI of 32' to include the wording 'obese'.
- Added 'You can close this browser window now' to the end of the online survey.

3.3.7 Questionnaire design and questionnaire delivery platform

Similar surveys in other developed countries using postal based questionnaires have yielded response rates below 50% (Oakley *et al.*, 2008, Bhattacharya *et al.*, 2009). To obtain a higher response rate an internet-based computerised questionnaire accessed via a secure internet site (provided by SurveyGizmo) was used. An Otago University web address and portal were used to brand the questionnaire and provide assurance to potential participants of the validity of the research and the security of their data. This method has been shown to be particularly useful when studying sensitive issues (Johnson *et al.*, 1994, van Roode, 2010). The very high recent internet access statistics in the region, upwards of 90% (Statistics New Zealand, 2010a), suggested that an online questionnaire would be suitable and convenient for most of the women. An online survey site (provided by SurveyGizmo) was, therefore, chosen to deliver the questionnaire. For women without access to, or preferring not to use, the internet two alternatives were offered: A telephone interview; or, in their final reminder letter, a short paper based questionnaire.

The fertility questionnaire was adapted from the following three validated surveys: The US Fertility and Family Growth Survey; the North East of Scotland Fertility Study; and the Dunedin Multidisciplinary Health and Development Study

(Chandra *et al.*, 2005, Bhattacharya *et al.*, 2009, van Roode, 2010). The demographic questions were refined for the New Zealand context, e.g. to include ethnicity data using the New Zealand census ethnicity questions. Service use questions were expanded to capture more detailed information and also a section added to collect information on knowledge and attitudes; these questions were adapted from Adashi *et al*. (2000).

The online questionnaire was structured to capture the most important details first (refer to Appendix B from page 319 for a full copy of the study questionnaire that was used to program the online questionnaire). Therefore, after logging in with a participant specific user identification (used in order to keep the dataset anonymous, but allow tracking of non-responders), women were asked their age, and then details of their fertility history, including number of pregnancies (if any). The first part of the questionnaire was then structured as follows:

- A set of questions for each pregnancy, which included whether they were trying to conceive, whether there were any difficulties in conceiving a pregnancy, and then any health services accessed.
- If health services were accessed, women were asked specifically what help was provided.
- For specialist services, women were asked whether they were given a diagnosis, and whether any treatment was received. Finally they were asked about total amount of time spent trying to conceive and how the pregnancy ended (unless it was a current pregnancy, in which case this question was not shown).
- For pregnancies occurring when they were not trying to conceive, the women were asked whether they had been having regular intercourse without contraception, and, if so, for how long before the pregnancy. Women were asked a very similar set of questions if they indicated they were currently trying, with slightly different wording (e.g. they were asked how long they had spent trying to conceive so far), and also if they had ever had a failed attempt to conceive.

- If women indicated they had a failed attempt to conceive (no pregnancy occurred) they were not asked whether they had difficulties conceiving. This question would possibly be insensitive, so the questionnaire was programmed assuming that they would have answered this question with a 'yes'.

This detailed fertility history provided all the information required to determine which women had infertility by various definitions, services sought and received for infertility and whether infertility was resolved (with a live birth).

The second part of the questionnaire was then structured as follows:

- Women were asked about future fertility plans.
- For those over 40 years old who did not indicate that they planned to have children in the future, they were asked whether they wished they had had more children (or any for childless women).
- All participants were asked a set of questions on conditions and procedures/operations that are related to fertility.
- All participants were asked a brief set of questions to assess fertility and fertility treatment knowledge and gauge views about funding of fertility treatment.
- Lastly women were asked a set of background questions such as relationship status, ethnicity, education and income.

Almost all questions in the survey were of a *radio button* (women select a single answer by clicking with their mouse on the response's button) or *check box* (allowing selection multiple responses to a question) nature.

For any women choosing a telephone interview, their interviewer (who was either the principal investigator or one of two other trained research interviewers) filled in the online questionnaire on their behalf during the interview.

A very brief paper-based survey was also produced to try to capture some infertility data from initial non-responders. This questionnaire was only one page long; it was designed to ascertain only whether women had had infertility that

lasted 12 months or more and whether this was primary or secondary infertility. Refer to Appendix C on page 333 for a copy of this questionnaire.

3.3.8 Enrolment procedures

The initial invitation for the study was by post (refer to Appendix D, page 335). A reminder letter was sent to non-responders approximately two weeks later. These letters informed potential participants about the study, and invited them to participate through a secure online questionnaire. They were also provided with a pre-paid return slip allowing them to decline further contact or ask to participate by CATI.

Following two letters, landline telephone numbers for non-responders were searched for in Telecom's *Whitepages*. Searching was first performed by women's surnames and then, if no listing was found, by any alternative surnames identified as residing at that address from the electoral roll. Women were then called to ascertain if they had received their invitation and offered either a telephone interview or an e-mail with information about the survey and a hyperlink to the survey (refer to Appendix E, page 337).

On 4 November 2011, a new electronic copy of the electoral roll was obtained, the Writ Day Electoral Roll. This is the final electoral roll prior to a general election, and due to the campaigning regarding enrolling to vote prior to an election, this roll is considered to be the most accurate and up-to-date electoral roll available. The Writ Day Electoral Roll was used to verify the current addresses for non-responders without a telephone number. For women who had changed address, recruitment was re-initiated from the beginning with an invitation letter. For those women whose addresses were unchanged, a third and final letter was sent that also included a short paper-based questionnaire. The envelope was also altered to include three tick boxes next to the addressee, to facilitate return or forwarding of unwanted mail. The tick box options on the envelope were: 'Return to sender, address unknown'; 'Return to sender, this is mail I do not want to receive'; and 'Please forward to the following address' (refer to Appendix F on page 339 to view

a scanned example of returned mail using this initiative, note that the name and address on the envelope have been obscured for privacy reasons).

3.3.9 Measures taken to improve response rates

A number of methods were researched and undertaken to improve response rates, many of which were based on recommendations for internet-based surveys by Fincham (2008), specific methods employed were:

- Invitations were personalised and the study clearly branded using the University of Otago letterhead and envelopes (the University is a well known, respected and trusted institution in the region).
- Endorsement of the research by Fertility New Zealand (a charitable organisation that provides support, advocacy and education on infertility) was included in the invitation letter.
- A tea bag (to acknowledge participation and personalise the letter) was included with the initial invitation letter.
- Entry into a draw for one of three $200 grocery vouchers upon survey completion was offered.
- A summary of the results, once available, was offered to each participant completing the survey.
- Awareness was increased though a media release on the University of Otago website, resulting in an interview on local television (Channel 9), newspaper articles (The Press, The Southland Times and various smaller weekend papers) and the study being reported on the news website www.stuff.co.nz.
- Addresses were verified for non-responders using a new copy of the electoral roll update for elections (the Writ Day Electoral Roll).
- Two reminder letters (three for non-responders if there was no telephone contact made) were sent.
- A reminder telephone call (and e-mail if preferred) was made if non-responders had a public telephone listing.

- Three different modes of survey completion were offered to increase convenience (online, telephone interview or paper based).

Enrollment procedures were initiated on 30 June 2011 and the sample was divided into four waves of collection approximately six weeks apart (in order to distribute a practicable workload). Data collection was completed and the online survey portal closed on 11 December 2011.

3.3.10 Data management

All data were stored securely online by SurveyGizmo, both for those entered directly by the participants and for those entered by the interviewers. A comma-separated file was downloaded twice weekly and stored on a secure server at the University of Otago. All survey data were delinked from any information that would allow identification of the participants. However, to facilitate monitoring of responses and follow up of non-responders, each survey response contained a unique identification code that had been assigned to each of the 2,200 randomly sampled women.

A list of the sampled women's names, ages, addresses, mesh block code (see Section 3.3.14 on page 86 for an explanation of the significance of this variable), Māori descent (a yes/no variable available with electoral roll data), unique identification code and participation status was stored separately to the survey data. Names and addresses were removed from this file once follow up was completed.

The final comma separated file to be downloaded was imported into STATA 12.1/SE for cleaning, labelling, validation and variable generation in preparation for analysis. The unique identification code was then used to merge the variables available via the electoral roll data (which were, therefore, available for both participants and non-participants) to the survey dataset. These variables were: Age; mesh block; responded (yes/no); received invitation (yes/no); eligible (yes/no) participated (yes/no); and the method of participation (online, CATI or postal). The unique identification code was also used to de-duplicate the dataset. Finally,

information from the postal surveys was double entered by two different people (to detect any data entry errors) in Microsoft Excel and imported into this dataset.

3.3.11 Derivation of fertility / infertility, fecundity and family formation variables

Variables measuring infertility and infecundity were based on the accepted and commonly used definitions presented in Table 1.1 on page 3. The construction of these variables using the survey data is presented in Table 3.1.

Table 3.1: Coding of infertility and infecundity measures from survey data

Definition and how it was derived	Eligibility
Ever tried to conceive for 12 months or more	
Coded as a 'yes' if reported a total time trying to conceive of at least 12 months for any failed pregnancy attempt, current pregnancy attempt, current pregnancy or previous pregnancy.	Must have had or tried to have a pregnancy. If not, the value of this variable was coded to missing.
Ever tried to conceive for 24 months or more	
Coded as a 'yes' if reported a total time trying to conceive of at least 24 months for any failed pregnancy attempt, current pregnancy attempt, current pregnancy or previous pregnancy.	Must have had or tried to have a pregnancy. If not, the value of this variable was coded to missing. Data not available for those who completed the paper-based questionnaire.
Ever had regular intercourse without contraception for 12 months or more	
Coded as a 'yes' if reported total time having regular sex without contraception was 12 months or more for current pregnancy, or any previous pregnancy, or any episode of regular unprotected intercourse the last 12 months or more without a pregnancy occurring. The variable was also coded to a 'yes' if 'ever tried to conceive for 12 months or more' was a 'yes', as it was assumed these women were not using contraception.	The value of this variable was coded to missing if questions were skipped on pregnancies and regular intercourse without contraception. Data not available for those who completed the paper-based questionnaire.
Ever sought medical help to conceive	
Coded as a 'yes' if they sought the help of a GP or other non-specialist, or a specialist for difficulties conceiving.*	Must have had or tried to have a pregnancy. If not, the value of this variable was coded to missing.

Table 3.1 ***continued***

Definition and how it was derived	Eligibility
Ever tried for 12 months or more, or sought medical help to conceive	
Coded as a 'yes' if either 'ever tried to conceive for 12 months or more' or 'ever sought medical help' was a 'yes'.	Must have had or tried to have a pregnancy. If not, the value of this variable was coded to missing.
Primary unresolved infertility	
Coded as a 'yes' if reported no pregnancies and reported wishing that they had had children and/or reported unsuccessfully attempting to become pregnant. This definition, therefore, will encompass some women who were not physically infertile, but infertile due to social circumstances.	Must be aged 40 or more years old.† If not, the value of this variable was coded to missing.
Involuntary childlessness	
Coded as a 'yes' if no live births and reported currently trying to conceive, wished she had had children, or planned to have children in the future	Must be aged 40 or more years old†, if not, the value of this variable was coded to missing. Data not available for those who completed the paper-based questionnaire.
Voluntary childlessness	
Coded as a 'yes' if no live births and 'no' for 'involuntary childlessness'	Must be aged 40 or more years old†, if not, the value of this variable was coded to missing. Data not available for those who completed the paper-based questionnaire.

* *Women were also asked about seeking help from non-medical health providers (e.g. naturopaths, homeopaths) but those who only obtained help from such practitioners were not considered to have sought 'medical' help.*

† *Primary unresolved infertility and voluntary/involuntary childlessness was considered in women aged 40 years and over only, as these women were likely to be nearing the end (or at the end) of their reproductive life span.*

A further fecundity related variable was created pertaining to having fewer children than desired. Any woman aged 40 or more years who was not planning any future pregnancies was asked 'Do you wish you had had more/any children?' Those who responded 'No, not at all' or 'A little' were considered to have attained desired family size, whereas those who responded 'Somewhat' or 'Yes, very much' were considered to have not attained desired family size. Women aged 40 or more years who planned to have children in the future, or were currently trying, were also considered to have not attained their desired family size.

Additional to the generation of these new variables, data for live births were also adjusted. A question on the total number of live born children was asked for those who had reported having one or more previous pregnancies. The number of pregnancies ending in a live birth was generated using the pregnancy specific questions and compared with reports of live births. It was assumed that the number of pregnancies ending in live birth should be the same, or, due to non-singleton births (such as pregnancies that ended with the birth of twins or triplets), slightly lower than the number of live born children.

There were three women who reported that their number of live births was one fewer than the total number of pregnancies that they had reported as ending in live birth. This result may have occurred due to either the respondents clicking the wrong radio button for the number of live born children question, or perhaps due to the death of a child. As such, the number of live born children for these women was recoded to match the number of pregnancies ending in live birth. Six women who skipped the live births question, but provided full data on pregnancies also had their live births data replaced by the number of pregnancies ending in live birth. All women who had not been pregnant, or reported no previous pregnancies (i.e. they were currently pregnant for the first time) were coded as having had no live births.

3.3.12 Adjustments to infertility service use questions

Amongst the questions on service use for their previous pregnancies, current pregnancy, current attempt to conceive and/or unsuccessful attempt to conceive, women were asked if they had seen a non specialist provider (e.g. a GP) and what help they were provided with. Women could give multiple responses to this question, the options being: Advice; testing; referral to an infertility specialist; referral to a gynaecologist; other (women were asked to specify details using a free text field if this was selected); and none (no other option could be selected if *none* was selected). Additionally, if women saw a specialist directly, or indicated they had been referred to one, they were asked what diagnoses they had been given, with the response options being: Ovulation problems; blocked fallopian tubes;

endometriosis; my partner had sperm problems; other (details were requested); and unknown (an exclusive option). Finally, they were also asked about treatment received from the specialist with the options being: Drugs; artificial insemination; *in vitro* fertilisation (IVF); surgery; other (details were requested); and none (exclusive option).

For the purposes of analysis, the specified other responses in these three questions were examined and recoded to another response option if appropriate. The response options to the first question, on services rendered by a non-specialist, were also recoded in order to include commonly specified services as follows: For services provided by a GP the two options of referral to an infertility specialist and to a gynaecologist were combined into one category. For the second question (on diagnoses) response options were recoded as follows: All ovulation related diagnoses specified were combined with ovulation problems to create *ovulation disorder*; all tubal problems (including sterilisation) were combined with blocked fallopian tubes to create *tubal disorder*; and all problems specifying the male partner (including vasectomies) were combined with my partner had sperm problems to create *male factor*. As all male factors were combined into one category, all other known diagnoses, including those remaining in the *other* category, could be defined as *female factor* infertility. For the third question (on treatment) response options were recoded as follows: IUI was included with AI and was relabelled AI/IUI (although technically IUI is a type of AI, it is the most common form of AI) and ICSI was included with IVF. IVF was not relabelled, as ICSI can only ever be performed as part of IVF treatment and is not commonly separated from non-ICSI IVF procedures in IVF statistics.

The *other* services, diagnoses and treatments specified by participants are listed in Appendix G from page 341 along with any recoding to the original responses.

As women could report about multiple experiences when they may have accessed services for infertility, and, therefore, report multiple times about the types of non-specialist services received, and any, diagnoses given and treatments received from specialists, *ever* measures across all reports were created. Meaning for example, that from the responses to 'What help did your GP provide?', the variable

'Ever received advice', 'Ever referred', 'Ever tested' etc. were coded by combing all reports from an individual woman who said she had seen a GP and received advice, referral or testing respectively. This is similar to how the 'Ever infertility' variables were created. For analysis purposes these data were then evaluated using both the data from women's first episode of infertility, and these 'ever' service use measures (combined from all episodes of infertility in an individual).

3.3.13 Coding and prioritisation of ethnicity

Two findings from the 2006 census questions on ethnicity showed that clarification and adjustments to raw ethnicity data were needed in order to effectively use these data. First, a finding common to previous censuses, 10.4% of the population reported belonging to at least two ethnic groups (Statistics New Zealand, 2007d). Second, the response 'New Zealander', a self-specified ethnicity when other ethnicity is selected in census, was the third most common ethnicity in the 2006 census after New Zealand European and Māori (refer to Table 3.2 for a break down of the common ethnicities in New Zealand) (Statistics New Zealand, 2007c). Given this unprecedented rise in the 'New Zealander' ethnicity, it is now recommended by Statistics New Zealand that an alternative grouping should be made with this group being incorporated in the European category (Statistics New Zealand, 2009). Therefore, it was considered that the most prudent approach regarding ethnicity classification was to group any 'New Zealander' responses with European ethnicity and not Other ethnicity.

Further to issues of grouping ethnicity responses, was the issue of prioritisation of ethnic groups. In order to simplify analysis of ethnicity, a prioritised ethnicity coding was devised by the Department of Statistics in 1993 and revised in 1996 (Department of Statistics, 1993). This classification assigns the ethnicity of a person who has given multiple responses to just one ethnicity, ensuring that the total number of responses equals the total population. The algorithm for assigning prioritised ethnicity is as follows:

- If New Zealand Māori was one of the groups reported, assigned to New Zealand Māori;

- Otherwise, if any Pacific Island group was reported, assigned to Pacific Island;
- Otherwise, if any Asian group was reported, assigned to Asian;
- Otherwise, if any group other than a European group was reported, assigned to other ethnic groups;
- Otherwise, assigned to European (including 'New Zealander').

The most appropriate method for the categorisation of multiple ethnicities is an on-going issue, with no single method identified to date that satisfies all users and uses of ethnicity data. Whilst prioritised ethnicity does not capture the ethnic diversity in New Zealand, it does provide a standardised, readily available and frequently used method to compare rates amongst broadly defined ethnic groups in New Zealand. A prioritised ethnicity grouping (as outlined above) was, therefore, applied to survey data ethnicity variables for the participant and her partner (if applicable) as aggregated ethnic groups in line with what has been commonly used in health research in New Zealand (Ministry of Health, 2010).

Table 3.2: Top 10 Ethnicities by total responses, 2006 Census

Ethnicity	2006 count
New Zealand European	2,381,076
Māori	565,329
New Zealander	429,429
Chinese	147,570
Samoan	131,103
Indian	104,583
Cook Islands Maori	58,009
Tongan	50,478
English	44,202
Korean	30,792

3.3.14 New Zealand deprivation index

All residential addresses, including those obtained from the electoral roll, can be mapped to non-administrative geographic areas of approximately 100 residents known as mesh blocks (Statistics New Zealand, 2013a). Mesh block code tables linking these mesh blocks to their 2006 New Zealand Deprivation Index Score data were obtained online (University of Otago, 2014). Mesh blocks can also be mapped to larger geographical areas, e.g. domicile areas (also non-administrative geographic areas, with 3,000–5,000 residents), regions and district health board (DHB) areas via the Annual Areas List (also available online).

Deprivation scores are relative measures of neighbourhood deprivation (area level scores), often used in health research in New Zealand as a surrogate marker for individual SES when patient's or participant's addresses are available. Commonly, for health data sets in New Zealand, these data are only available at a domicile area level and not at the higher resolution of mesh block. The deprivation score is a composite measure of nine variables from the five-yearly New Zealand census, which reflect different dimensions of deprivation (Salmond and Crampton, 2012). These dimensions and their census measures are shown in Table 3.3.

Deprivation scores are on an ordinal scale ranging from one to 10, where one represents the areas with the 10% least deprived scores, and 10 represents the areas with the 10% most deprived scores. This measure is also often referred to as the New Zealand Deprivation Index, and usually any reference includes the census year from which the measure was derived. So, the deprivation score calculated from the 2006 census for a person living in a particular domicile area, is referred to as the *NZDep06* score. NZDep06 scores were grouped into three categories (due to the moderate sample size) for use in analyses as follows:

- Low (deprivation deciles 1–3).
- Medium (deprivation deciles 4–7).
- High (deprivation deciles 8–10).

Table 3.3: Census variables used to create deprivation scores

Dimension	Census variable
Income	People aged 18–64 years receiving a means tested benefit.
Income	Equivalised* income below an income threshold.
Owned home	People not living in own home.
Support	People aged <65 years living in a single parent family.
Employment	People aged 18–64 years unemployed.
Qualifications	People aged 18–64 years without any qualifications.
Living space	People living in equivalised* households below a bedroom occupancy threshold.
Communication	People with no access to a telephone.
Transport	People with no access to a car.

* *Equivalisation: method used to control for household composition.*

3.3.15 Derivation of other variables

Education

Education was measured based on highest level of qualification achieved. All those specified 'other' for highest qualification were examined to see whether responses could be recoded into a qualification level. For example, the response provided of 'some completed uni courses and 7thform [*Sic*] bursary' could easily be reclassified, in this case into the category New Zealand university bursary/scholarship/NCEA level 4. Following this, education was grouped into three levels, being: High school or less; post high school, but not university (this included polytechnic qualifications, trade certificates and vocational training); and university (which included both undergraduate and post-graduate degrees/diplomas).

Income

Income was based on annual household income. The original income question had six categories; these were combined into three, being: Low (up to and including $30,000); Medium ($30,001–$70,000); and high (above $70,000). The income grouping for the survey question was based on supplementary data tables showing the distribution of income in New Zealand that were provided with the New Zealand Income Survey (Statistics New Zealand, 2010b).

Body mass index

As imperial measures are still commonly referred to and used in New Zealand, for questions on height and weight participants were given the option to respond in either imperial or metric units. Imperial units were converted to the metric units required to calculate BMI as follows:

- Feet were converted to centimetres by multiplying by 30.48, inches to centimetres by multiplying by 2.54 and centimetres to metres (m) by dividing by 100.
- Stones were converted to kilograms (kg) by multiplying by 6.35 and pounds to kg by dividing by 2.20.

BMI was calculated as weight (in kg)/height (in metres)^2 and then, according to World Health Organization guidelines (2014), categorised as follows:

- Underweight (<18.5 kg/m^2).
- Normal (18.5–24.9 kg/m^2).
- Overweight (25.0–29.9 kg/m^2).
- Obese class I (30.0–34.9 kg/m^2).
- Obese class II (35.0–39.9 kg/m^2).
- Obese class III (≥40.0 kg/m^2).

Smoking

Women who reported being current smokers were coded as such, those who reported smoking previously were considered to be *past smokers* and those who

said ‘no’ to previously smoking as *never smokers*. Those who said they did not currently smoke, but skipped the question on past smoking were also considered to have never smoked.

3.3.16 Statistical description of the data

A flow diagram was constructed showing the numbers of women receiving the initial study invitation letter, the first reminder letter, a telephone reminder and a final reminder including the brief paper-based questionnaire. The number of responses by response type and proportion participating at each of these follow up phases as well as in total were presented in the flow diagram.

The proportion of the sample that participated was calculated in two ways. First, by only removing those found to be ineligible (due to being male, having an address outside the region, or not being capable of completing the survey) from the denominator (the eligible sample). Second, by removing both those who were ineligible and those known not to have received the study invitation. Basic demographic characteristics available from the electoral roll, either directly or indirectly though linking with the annual areas and domicile tables, were compared for participants and non-participants amongst the eligible sample. The remaining basic demographic characteristics that were not available for non-participants (relationship status, prioritised ethnic group, highest qualification and annual income), risk factors for infertility and procedures/conditions that can effect fertility were then tabulated for the survey participants.

The prevalence of infertility by various definitions of infertility was calculated with 95% CIs computed using the binomial distribution. The clinical/epidemiological definition of infertility was compared with self-defined difficulties conceiving, seeking non-medical help, seeking non-specialist and specialist medical help, whether a live birth was achieved following the episode of infertility and whether the desired family size was achieved. These comparisons were limited to women’s first experience of infertility if they had experienced more than one episode. A flow chart was used to describe the sequence, and associated prevalence, of women who tried to get pregnant, experienced difficulty, sought medical help, got referred

to specialist services, received treatment and resolved infertility. Ovulation monitoring behaviours and general knowledge/attitudes towards fertility were described for the sample.

All differences between categorical data were tested using Pearson's χ^2 tests and, where there were ordered categorical variables, χ^2 tests for trend were performed. Additionally, binomial probability tests were performed to assess whether the proportions correctly answering the multi choice knowledge questions were significantly different from that expected by chance. All analyses were conducted in STATA 12.1/SE.

3.3.17 Poisson regression modelling

Following the basic statistical description of the survey data, analyses of infertility prevalence, use of health services and resolution of infertility amongst study participants followed the plan summarised in Figure 3.1. The overall aim of this plan being to determine at each of these stages in this pathway what factors were associated with progressing to the next stage (e.g. what differentiates women who have infertility and seek service from those who do not seek service). Prior to regression modelling, outcome prevalence was described by demographic variables, which were: Relationship status; age group; aged 35 of more at onset of first infertility; ethnicity; NZDep06; educational level; and household income. They were also described by smoking and BMI, two well-known risk factors for infertility, which are also related to service access in New Zealand.

Poisson regression was chosen in order to estimate relative risk directly, as logistic regression would have given odds ratios that do not approximate well to relative risk given the high prevalence of the outcomes being examined (Barros and Hirakata, 2003, McNutt *et al.*, 2003, Zou, 2004). The model was used without an offset (so time to event was not considered in the model, as is appropriate in a cross-sectional study), thereby modelling a risk ratio (RR) analogous to a ratio of the prevalence of the outcomes in the exposed and unexposed groups. To compensate for the over estimated errors when Poisson regression is used to estimate a common outcome, robust standard errors were applied.

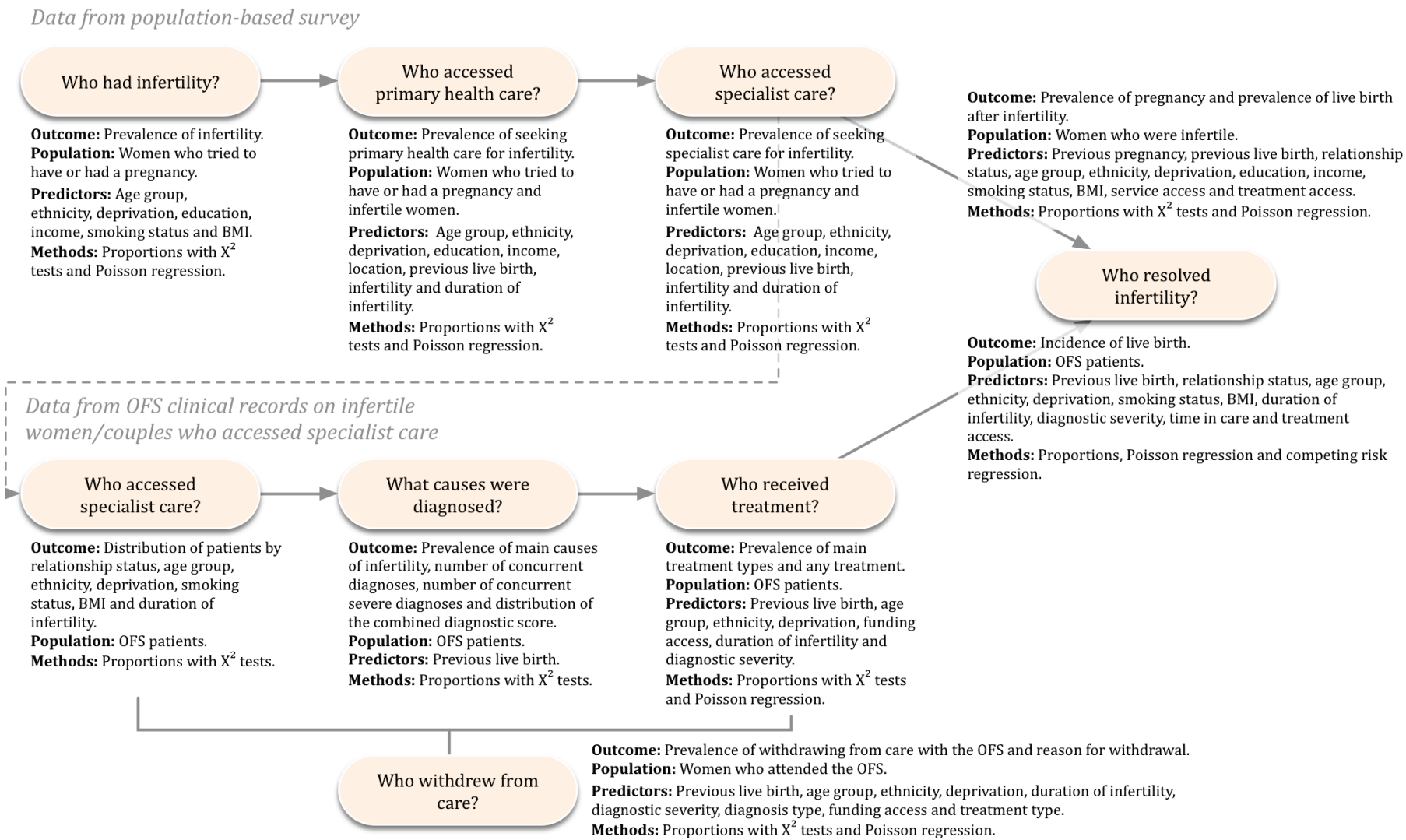


Figure 3.1: A cascade of infertility information: analysis plan for survey and OFS data on infertility

Following the unadjusted assessment of the association between the four outcomes (had infertility, sought non-specialist services, sought specialist services and resolved infertility) and the independent variables, the independent variables were then selected for testing in the multivariate model based on having a Wald test p-value of less than 0.20.

An adequate number of events per independent variable were required to avoid an overfit model. Commonly recommended minimums range from 10 to 20 events per covariate; for this analysis a cautious approach of at least 20 events per covariate was chosen to improve model validity (Feinstein, 1996, Peduzzi *et al.*, 1996). Therefore, some categorical variables were collapsed or added as a linear term to reduce the number of covariates to a maximum of 12 for the infertility model, seven for ever seeking primary health care, five for ever seeking specialist care and eight for the infertility resolution model.

A standard sequential model building strategy was employed (Hosmer *et al.*, 2013). The selected variables were added sequentially to the model based on an *a priori* hypothesis of relative importance. To determine if each additional variable significantly improved the model, the models were compared stepwise using the Akaike information criterion (AIC). Likelihood ratio tests could not be performed due to the use of robust standard errors. No adjustments for multiple comparisons were made, as this was an exploratory analysis.

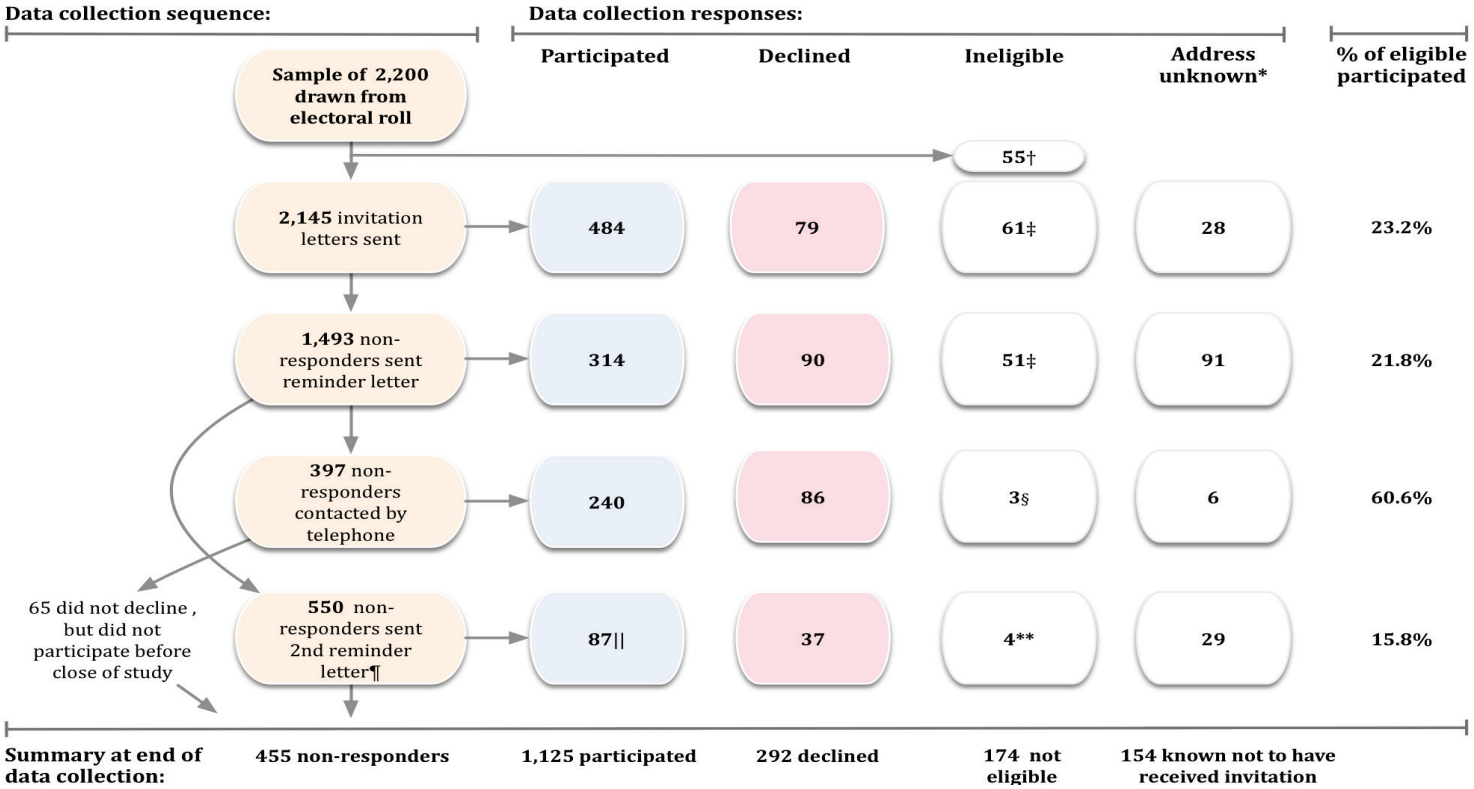
Internal validity for each final model was formally quantified by using the bootstrapping method for regression. Each categorical parameter in each model was also checked for overall significance using Wald tests. The crude and adjusted RRs, as well as the 95% CIs and Wald test p-values (calculated with robust standard errors) were reported.

3.4 Results

3.4.1 Participation

Figure 3.2 on the next page shows the data collection process and responses at each stage. Of 2,200 women drawn from the sample, at the end of data collection 2,026 were eligible. The status of 455 non-responders could not be verified, but they were assumed to be eligible and received an invitation to complete the questionnaire. A further 154 women were assumed not to have received the survey, based on information from either *return to sender* post, telephone/e-mail contact from residents at the address, or through address verification from the updated Writ Day electoral roll (they could no longer be traced). After the initial invitation and two further attempts to contact non-responders, the total number of participants was 1,125 (55.5%). If the 154 women who were known not to have received the questionnaire (those returned with no known address) were excluded from the denominator, then the proportion that participated increased to 60.1%.

Age, Māori descent, rural vs. urban residential area and deprivation score were available for all women in the sample (participants and non-participants) as these data were derived from the Electoral Roll. Table 3.4 on page 95 compares these characteristics for participants and non-participants amongst women who were eligible to participate in the study. There was some variation in participation, with lower participation amongst those aged 25–29 years, those of Māori descent and those from high deprivation areas. Although none of these groups had very poor participation, the differences between participants and non-participants were statistically significant for all four variables (Pearson's χ^2 all $p \leq 0.05$).



* *Unknown due to return to sender mail with no forwarding address and/or could not be found on the Writ Day electoral roll.*

† *Identified as ineligible prior to mail out of invitation letter due to address outside region (n=22) or male (n=33).*

‡ *Identified as ineligible due to address outside region during enrolment procedures either by contact from current residents at the address or noted when envelopes for mail outs were being labelled.*

§ *Identified by telephone interviewer contact as ineligible due to intellectual comprehension (n=1), language ability (n=1) and residing overseas (n=1).*

¶ *Non-responders for whom no telephone listing could be found or for whom no phone contact could be made.*

|| *63 participated by returning a completed short paper based questionnaire.*

** *Four women were found to have an address outside the region when their address mesh blocks were linked to regions and DHB via the Annual Areas List.*

Figure 3.2: Data collection stages and responses by stage

3.4.2 Demographic characteristics of participants

Table 3.4 describes the demographic characteristics of the participants (and also non-participants where data were available, as described in the previous section).

Table 3.4: Demographic characteristics of participants and non-participants

		Participants, n (%)		Non-participants, n (%)		P-value
Total, N		1,125		901		
Age group (years)	25–29	215	(19.1)	210	(23.3)	
	30–34	159	(14.1)	98	(10.9)	
	35–39	208	(18.5)	177	(19.6)	
	40–44	277	(24.6)	203	(22.5)	
	45–50	266	(23.6)	213	(23.6)	0.047
Current relationship status	Married/cohabiting with male partner	837	(74.4)	–		
	Male partner, not living together	49	(4.4)	–		
	Civil union/cohabiting with female partner	5	(0.4)	–		
	Not in a relationship	151	(13.4)	–		
	Missing*	83	(7.4)	–		
Māori descent	Yes	109	(9.7)	133	(14.8)	
	No	1,016	(90.3)	768	(85.2)	<0.001
Prioritised ethnicity of participant	European	981	(87.2)	–		
	Māori	78	(6.9)	–		
	Pacific peoples	3	(0.3)	–		
	Asian	20	(1.8)	–		
	Other	15	(1.3)	–		
	Missing	28	(2.5)	–		

Table 3.4 *continued*		Participants, n (%)		Non-participants, n (%)		P-value
Prioritised ethnicity of participant's partner†	European	792	(70.4)	–		
	Māori	50	(4.4)	–		
	Pacific peoples	11	(1.0)	–		
	Asian	14	(1.2)	–		
	Other	16	(1.4)	–		
	Missing*	8	(0.8)	–		
Rural/ urban residence	Urban	898	(79.8)	771	(85.6)	
	Rural	227	(20.2)	130	(14.4)	0.001
Deprivation (NZDep06)	Low (deciles 1–3)	512	(45.5)	338	(37.5)	
	Medium (deciles 4–7)	429	(38.1)	335	(37.2)	
	High (deciles 8–10)	184	(16.4)	228	(25.3)	<0.001
Highest qualification level	High school or less	436	(38.8)	–		
	Post high school, not university	255	(22.7)	–		
	University	338	(30.0)	–		
	Missing as response was not categorisable	12	(1.1)	–		
	Missing*	84	(7.5)	–		
Annual household income (NZD)	Low (≤ $30,000)	124	(11.0)	–		
	Medium ($30,001–$70,000)	392	(34.8)	–		
	High (>$70,000)	479	(42.6)	–		
	Missing*	130	(11.6)	–		

– *These data were not available for non-participants.*

* *Missing value includes 63 women who completed the much shorter paper-based questionnaire, which did not include this question.*

† *Only those who reported having a current partner were eligible for this question.*

Almost half (48.2%) of the participants were aged 40 or more years. Three-quarters of participants were married or cohabiting with a male partner. The vast majority (87.2%) were of New Zealand European or European ethnicity, as were the partners of participants (70.4% were European). More women were reported

as having Māori descent on the Electoral Roll than self-reported Māori ethnicity in the survey (9.7% vs. 6.9% respectively). One-fifth (20.2%) of participants lived in rural locations and just 16.2% of participants were from high deprivation areas. More than half of the participants had post high school qualifications, with 30.0% having university qualifications. Income information paralleled the deprivation data, with few participants classified as having low income (11.0%).

3.4.3 Fertility and reproductive health characteristics of participants

Table 3.5 on the next page describes the reproductive characteristics and prevalence of infertility risk factors amongst the participants.

Most (86.6%) of the women who participated had 'tested their fertility', meaning they had had a pregnancy, or attempted to conceive. Slightly fewer women in the sample reported a pregnancy (82.2%), and slightly fewer again reported a live birth (75.3%).

The prevalence of their infertility risk factors, current smoking and being underweight or obese (based on BMI calculated from self reports of weight and height), was relatively low (13.2%, 1.2% and 21.8% respectively).

The prevalence of most procedures that effect fertility was also low, the most common response selected being 'other'. Women commonly specified this procedure as laparoscopy, caesarean sections, treatment for abnormal cervical cells, terminations and removal of tubes, fibroids and polyps (not all of which necessarily affect fertility). Vasectomies in women's partners were relatively common: 242 (27.3%) of the current male partners had had a vasectomy, although three (1.2%) of these men had had their vasectomies reversed.

The prevalence of conditions affecting fertility was also low in the sample, with endometriosis being diagnosed in 70 (6.2%) women and past STIs in 165 (14.7%). Other problems were reported by 132 (11.7%) women, the majority of these related to abnormal cervical smears, although reporting of irregular/heavy menstrual periods, ovarian cysts and damaged tubes was also common.

Table 3.5: Fertility and reproductive health characteristics of participants

		n	(%)
Total participants, N		1,125	
Ever tested fertility	Yes	974	(86.6)
	No	151	(13.4)
Ever pregnant	Yes	925	(82.2)
	No	200	(17.8)
Number of live births	None	278	(24.7)
	1	177	(15.7)
	2	382	(34.0)
	3	183	(16.3)
	4	69	(6.1)
	≥5	36	(3.2)
Smoking status	Current smoker	148	(13.2)
	Past smoker	307	(27.3)
	Non smoker	593	(52.7)
	Missing*	77	(6.8)
BMI category (in kg/m2)	Underweight, <18.5	14	(1.2)
	Normal, 18.5–24.9	484	(43.0)
	Overweight, 25.0–29.9	233	(20.7)
	Obese class I, 30.0–34.9	139	(12.4)
	Obese class II, 35.0–39.9	74	(6.6)
	Obese class III, ≥40.0	31	(2.8)
	Missing*	150	(13.3)
Procedures related to or that may affect fertility†	Chemotherapy	10	(0.9)
	Sterilisation	92	(8.2)
	Operation on ovaries	61	(5.4)
	Appendectomy	100	(8.9)
	Hysterectomy	50	(4.4)
	Other operation below abdomen	196	(17.4)
	Missing*	91	(8.1)

Table 3.5 *continued*		n (%)	
Partner has had vasectomy‡	Yes	239	(27.0)
	Yes, but reversed	3	(0.3)
	No	631	(71.2)
	Don't know	10	(1.1)
	Missing	3	(0.3)
Diagnosed conditions that may affect fertility†	Polycystic ovary syndrome	53	(4.7)
	Pelvic inflammatory disease	15	(1.3)
	Endometriosis	70	(6.2)
	Fibroids	52	(4.6)
	Sexually transmitted infection(s)	165	(14.7)
	Other gynaecological problem	132	(11.7)
	Missing*	94	(8.4)

* *Missing value includes 63 women who completed the much shorter paper-based questionnaire, which did not include this question.*

† *Multiple answers were possible.*

‡ *Only those who reported having a current partner were eligible for this question.*

3.4.4 Prevalence of infertility

Table 3.6 (on the next page) describes the prevalence of infertility and infecundity by the various definitions set out in Table 1.1 on page 3 and described in Table 3.1 on page 80, and also self-defined difficulty conceiving.

There were 974 women who had tried for or had a pregnancy; of these 211 (21.7%, 95% CI 19.1–24.4%) had tried for at least 12 months on one or more occasions to get pregnant. Women who only completed the paper questionnaire were not asked about trying to conceive for 24 months or more; of the remaining 911 fertility-tested women, there were 117 (12.8%, 95% CI 10.7–15.2%) women who had tried for at least 24 months to conceive on at least one occasion. While not a commonly reported measure, self-defined difficulty conceiving was also elicited from the fertility-tested women who completed the online questionnaire; 205 (22.5%, 95% CI 19.8–25.3%) reported that they had had difficulty conceiving.

Table 3.6: Prevalence of infertility and infecundity

Definition of infertility/infecundity	No. of events	Total no. of women	Prevalence %	(95% CI)
Ever tried unsuccessfully to conceive for 12 months or more	211	974	21.7	(19.1–24.4)
Ever tried unsuccessfully to conceive for 24 months or more	117	911	12.8	(10.7–15.2)
Self-defined difficulty conceiving	205	911	22.5	(19.8–25.3)
Ever had regular unprotected intercourse for 12 months or more without conceiving	327	1,056	31.0	(28.2–33.8)
Ever sought medical help to conceive	171	974	17.6	(15.2–20.1)
Ever tried for 12 months or more, or sought medical help to conceive	246	974	25.3	(22.6–28.1)
Primary unresolved infertility	9	476	1.9	(0.9–3.6)
Involuntary childlessness	35	518	6.8	(4.8–9.3)
Voluntary childlessness	36	518	7.0	(4.9–9.5)

Another commonly used measure to describe infertility, spending 12 months or longer having regular intercourse without contraception (which by definition includes those women who tried to conceive for 12 months or longer), yielded a prevalence of 31.0% (95% CI 28.2–33.8%) amongst 1,056 women (this analysis was not limited to women who had tried to or had conceived).

Seeking medical help for difficulties conceiving was reported by 171 (17.6%, 95% CI 15.2–20.1%) of the 974 women who had tried to or had conceived. Although a further 10 women also reported seeking medical help for infertility, these reports were not related to a specific attempt to conceive and two of these 10 women had not had or attempted to have a pregnancy. When considering seeking medical help to conceive together with trying to conceive for 12 months or more, 246 (25.3%, 95% CI 22.6–28.1%) women had experienced infertility. Overall, amongst these 246 women, based on their earliest reported infertility experience, 135 (54.9%) had primary infertility and 111 (45.1%) had secondary infertility. The age for the first episode of infertility ranged from 17–42 years with a median of 28 years in the whole sample. There were 137 women with infertility who were aged 40 years

or more when they completed the survey (and, therefore, less likely to experience infertility for the first time after completion of the survey), the median age of first infertility was slightly older for these women (29 years).

Of 235 women who completed the computerised questionnaire and met the *tried for 12 months or sought medical help* definition of infertility, 50.6% reported one episode of infertility. Most other women reported two to four episodes of infertility, but seven women reported between five and seven episodes.

Amongst the 476 women who had ever tried to or had conceived who were aged 40 years or more, nine (1.9%, 95% CI 0.9–3.6%) had primary unresolved infertility and 27 (5.7%, 95% CI 3.8–8.1%) were involuntarily childless. If the definition of involuntary childlessness is expanded to incorporate those who had not previously tried to have a child, whose infertility was possibly due to social causes (e.g. not having a suitable male partner), then 35 (6.8%, 95% CI 4.8–9.3%) of 518 women aged 40 years or more were involuntarily childless. Amongst these 518 women, there were also 36 (7.0%, 95% CI 4.9–9.5%) women who were voluntarily childless.

3.4.5 Service seeking, treatment and resolution of infertility: A description of women's first episode of infertility

A full pathway for seeking services, services received and outcomes for women who ever met the definition of infertility (being defined as 12 months of trying or seeking medical help to conceive) is described in Figure 3.3 on page 104 for their first episode of infertility. This figure only includes women completing the computerised questionnaire due to the limited number of items asked on the brief paper-based survey form.

There were 235 women who had one (or more) episodes of infertility. When considering just their first episode of infertility, 37 (15.7%) did not consider that they had a fertility problem. This result would suggest that their perception of difficulty was strongly related to the fact that all of these women had a pregnancy and all but two of these women went on to have a live birth either of this

pregnancy attempt or at another attempt after this first infertility episode. Of the 198 women who reported having difficulties, 144 (61.3% of the 235 infertile women) sought help by consulting a non-specialist, and 10 (4.3%) by consulting a specialist directly. Over a quarter of women who sought medical help tried to conceive for less than six months before seeking medical help or sought help before trying (41 of 152 who answered this question, 27.0%), 33 (21.7%) tried for 6–11 months, 51 (33.6%) for 1–2 years and 27 (17.8%) tried for over two years. However, if this is limited to the 19 women who were aged 35 or more years at their first occurrence of infertility, the proportion trying for less than a year is considerably higher (13, 68.4%).

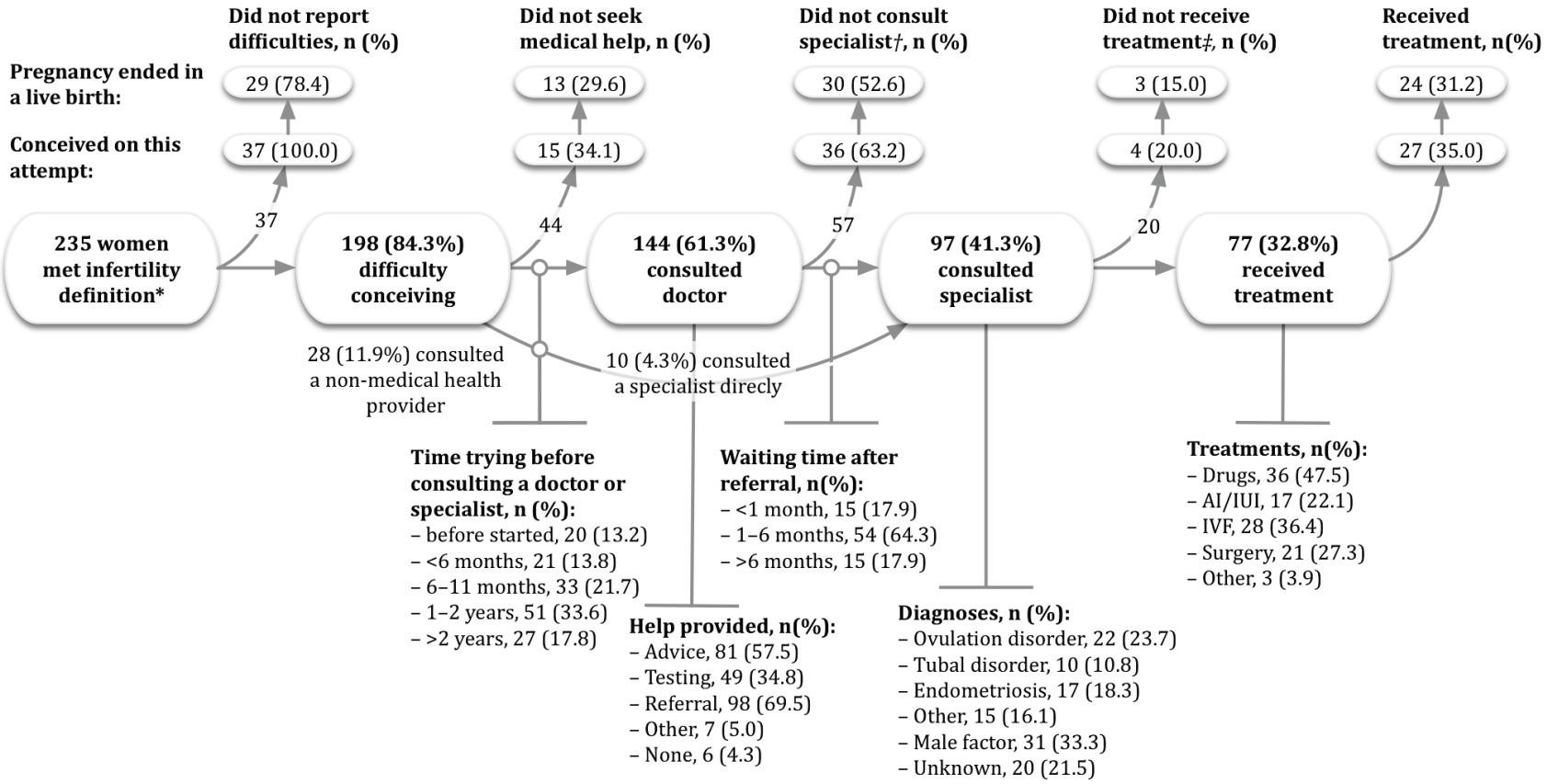
Of the 144 women who saw a non-specialist medical provider, 141 provided information about services rendered. Over half received advice (81, 57.5%) and just over two-thirds (98, 69.5%) were referred to specialist services. Although seeking medical services was not associated with infertility type (primary or secondary), being referred to specialist services was associated with infertility type. Of the 85 women with primary infertility, 67 (78.8%) were referred, whereas 31 (55.4%) of the 56 women with secondary infertility were referred (Pearson's χ^2 p=0.003). This association is slightly more pronounced when comparing women who had had a live birth (not all women with secondary infertility had had a live birth) with those who had not had a live birth before their first episode of infertility. Of women who had not had a live birth 80 (76.9%) of 104 women were referred, and for those who had had a live birth 18 (48.6%) of 37 were referred (Pearson's χ^2 p=0.001). Time trying before seeking help was also strongly associated with referral, with those who sought help before trying and those who waited 1–2 years being more likely to be referred than those waiting 0–12 months or more than two years (Pearson's χ^2 p=0.024). However, there was no relationship between infertility type and time spent trying before seeking medical help (Pearson's χ^2 p=0.512), so time waiting before seeing the specialist does not explain the difference in referral for women with primary vs. secondary infertility.

Of the 98 women who were referred to specialist services, 11 got pregnant before seeing a specialist, leaving 87 referred women who actually saw a specialist.

Including the 10 women who presented directly to a specialist with those who were referred, a total of 97 women (41.3% of those with infertility) saw a specialist. Amongst these women, male factors were the most common cause of their infertility (31 [33.3%] of the 94 women who provided information on diagnoses), followed by ovulation disorder (22, 23.7%). Twenty of 97 women who saw a specialist reported not having any treatment, although four of these women reported getting pregnant before any treatment could be started. These four women all had a live birth, as did seven other women who did not receive treatment.

The remaining 77 women (32.8% of those who had infertility) received treatment for their first episode of infertility, the most frequent treatments being drugs (36, 47.5%) and IVF (28, 36.4%). There were 16 pregnancies attributed to any treatment and two where women were not sure if the pregnancy was treatment related. All of these women resolved their infertility. Three-quarters (55, 75.3%) of women who had treatment did not have a pregnancy related to treatment, however, 29 of these 55 women did resolve their infertility.

Altogether, for 119 (50.6%) women their first episode of infertility ended with a pregnancy, with 99 of these resulting in live births. Another 79 women resolved their infertility with a pregnancy ending in live birth subsequent to this attempt. Therefore, in total 178 (75.7%) women resolved their first episode of infertility. Five of the 57 women who had not resolved their infertility were pregnant at the time they completed the survey, and a further 19 were trying to become pregnant. Thirty-nine of these 57 women had not had a live birth previous to their infertility; therefore, they were also involuntarily childless at the time they completed the survey. There was a small difference in resolution by whether infertility was primary or secondary (80.0% versus 70.5% respectively), which was not statistically significant (Pearson's χ^2 p=0.090). Those who were aged 35 or more years when they first experienced infertility were significantly less likely to have resolved their first episode infertility compared with those aged less than 35 years (57.1% versus 79.0% respectively, Pearson's χ^2 p=0.005).



* *Defined as 12 months or more trying or seeking medical help to conceive.*

† *Includes 11 referred women (11.3% of the 98 referred) who conceived before seeing specialist, 10 of whom eventually had a live birth and one who did not.*

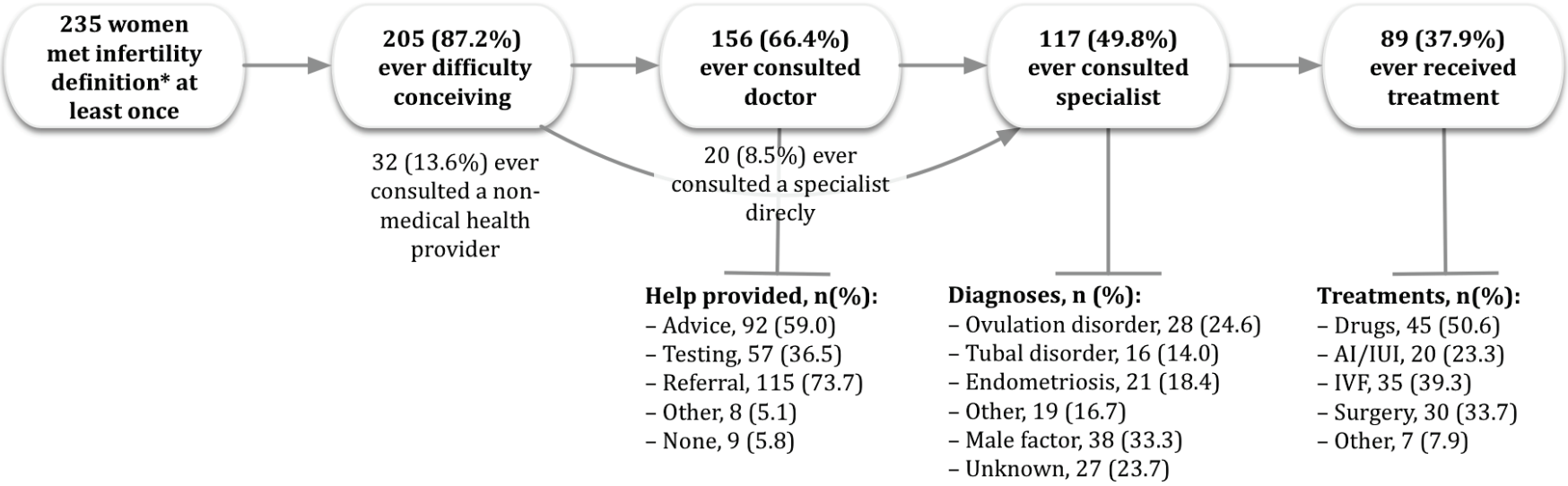
‡ *Includes four women who conceived before starting any treatment, all of whom eventually had a live birth.*

Figure 3.3: Access to services, uptake of treatment and resolution for the first experience of infertility

3.4.6 Services and treatment ever received for women with infertility and all women who tried to conceive or had a pregnancy

Figure 3.4 (overleaf) considers all reports from women with multiple episodes of infertility (defined as 12 months of trying or seeking medical help to conceive). The figure describes services sought, help received, diagnoses and treatment received ever (data combined for all episodes of reported infertility) for women defined as infertile. Again, the figure only includes women who completed the computerised questionnaire. Other aspects of service use available from the computerised questionnaire, such as time trying to conceive before seeking help, waiting time after referral to see a specialist and whether women resolved this episode of infertility with a live birth (and where on the care pathway this occurred) cannot be meaningfully combined into *ever* measures across multiple episodes and were not included in the figure.

Of the 911 women completing the computerised questionnaire, who had been or ever tried to be pregnant, 232 (25.5%, 95% CI 22.6–28.4%) reported ever considering themselves to have had difficulty conceiving (reported difficulty conceiving for one or more of their pregnancies, or a failed attempt to conceive). Amongst women who reported infertility of 12 months or more, or seeking medical help to conceive, 205 (87.2%) had ever considered that they had difficulty conceiving. Only 4.0% of women who did not meet this definition of infertility considered they had had difficulty conceiving. When considering the alternative definition of 24 months or more trying, a somewhat higher proportion of infertile women considered they had had difficulties (94.0%). However, the proportion of women reporting difficulties who were not considered infertile by this definition was almost four times higher than that for the 12-month definition (15.4%).



* *Defined as 12 months or more trying or seeking medical help to conceive.*

Figure 3.4: Ever reported difficulties conceiving, sought services or received treatment for all episodes of infertility

Only a small proportion of women who had infertility had ever sought help from a non-medical health provider (32, 13.6%), and of women who did not meet the infertility definition, only one more woman had seen a non-medical health provider. Almost three-quarters of women experiencing infertility sought medical help with 146 (62.1%) women ever entering care through visiting a non-specialist, 10 (4.3%) women entering care by going directly to a specialist and a further 10 (4.3%) women who had entered care both via visiting a non-specialist and directly with a specialist. This equates to 70.6% of the 235 women who had infertility seeking medical help to conceive.

The most frequent services provided by non-specialist doctors were referral and advice, with 115 (73.7%) and 92 (59.0%) of women who sought the help of a non-specialist receiving these services respectively. Very few women (9, 3.8%) with infertility reported seeing a non-specialist service provider and receiving no help.

Either directly or via referral, 117 (49.8%) women with infertility ever saw a specialist provider of services for fertility. Almost two-thirds of women did not have a diagnosis as they did not see a specialist (121, 51.5%) or the cause of their infertility was unidentified (27, 11.5%). The most common diagnoses received from specialists were male factor infertility (38, 16.2% of the 235 women with infertility) and ovulation disorder (28, 11.9%). Endometriosis was reported as a diagnosis received from a fertility specialist by 21 (8.9%) infertile women, however, a further 11 women with infertility reported endometriosis as a diagnosed condition when they were answering a general question about their health. This information was not available for other diagnoses.

Combining information from the five diagnostic categories (excluding unknown) shows that overall 63 (26.8%) women with infertility were diagnosed with one known factor, 25 (10.6%) with two known factors and three (1.3%) with three known factors. Female factor infertility alone (ever reported ovulation disorder, tubal disorder, endometriosis and/or other, but never male factor) was diagnosed in 53 (22.5%) infertile women, male factor alone was reported by 25 (10.6%) and combined male and female factors by 13 (5.3%).

Fertility treatment was received by 89 women (37.9% of those with infertility, 9.8% of all women who had been or tried to be pregnant). Drugs were the most commonly received treatment (45, 19.2% of infertile women), followed by IVF (35, 14.9%). Of infertile women, 27 (11.5%) attended a specialist, but received no treatment on at least one occasion. Of those who ever received treatment, 47 reported having a treatment related pregnancy (20.0% of infertile women, 5.2% of all women who had tried for or had a pregnancy).

3.4.7 Infertility and desired family size

Of the 494 women who were aged 40 years or more and who did not report any current or future plans to conceive, 245 (49.6%) did not want any/more children and 114 (23.1%) reported wanting any/more children only 'a little'. Over a quarter of these women who were most likely nearing, or had already reached, the end of their reproductive potential, reported desiring more children than they had had. There were 64 (13.0%) women wishing 'somewhat' that they had had any/more children and 71 (14.4%) wishing this 'very much'. These 135 women were considered overall to have wanted any/more children and, therefore, had not reached their desired family size.

Amongst these 135 women, 46.5% of the women who had two or more live births reported wanting more children very much compared with 53.9% and 68.0% for women with one live birth and without a live birth respectively. However, this trend was not statistically significant (χ^2 test for trend $p=0.067$). Overall, the number of live births was strongly related to women reporting having not reached their desired family size (Pearson's χ^2 $p<0.001$); while just 19.2% (71) of women with two or more children wished that they had had more children, this was reported by 59.1% (39) of those with one live birth, dropping to 43.1% (25) among women with none.

Women were twice as likely to report not having reached their desired family size if they had ever experienced infertility lasting for 12 months or more, or needed medical help to conceive. Amongst women who had experienced infertility 50 (40.7%) did not reach their desired family size, whereas amongst women who had

not experienced infertility 76 (22.6%) did not reach their desired family size (Pearson's χ^2 p<0.001). Overall, amongst all women who had ever tried to have or had a pregnancy, having less than two live births was associated with a higher prevalence of infertility; 42 (33.1%) women with no live births and 58 (32.8%) women with one live birth had experienced infertility, whereas 146 (21.8%) women with two or more children had experienced infertility (Pearson's χ^2 p=0.001). These differences were more evident amongst women aged 40 or more years who had finished their childbearing, with 14 (58.3%) women who had no live births having had infertility, 23 (34.9%) women who had one child having had infertility and 86 (23.2%) women with two or more live birth having had infertility (Pearson's χ^2 p<0.001).

3.4.8 Fertility intentions

Of the 1,053 women who answered questions on future plans to have children 40 (3.8%) were currently trying to conceive, 185 (17.6%) planned to have children in the future, 758 (72.0%) did not intend or could not have children in the future and a further 70 (6.7%) women were unsure.

Table 3.7 on the next page shows the number of women who were currently trying to have or planning to have children in the future by the number of previous live births and age group.

There was a significant trend of decreasing proportions of women reporting future childbearing intentions with number of live births (χ^2 test for trend p<0.001).

The proportion of women who were trying to have or planned to have children in the future decreased with increasing age (χ^2 test for trend p<0.001), this trend by age was just as evident amongst the 257 women who had not reported a live birth (χ^2 test for trend p<0.001).

Table 3.7: Intention to have children in the future by number of previous live births and age group

		Currently trying or plan to have future children n (%)		χ^2 test for trend P-value
Number of live births	None	140	(54.5)	
	One	52	(31.0)	
	Two	28	(7.8)	
	Three or more	5	(1.9)	<0.001
Age group (years)	25–29	141	(70.2)	
	30–34	52	(34.2)	
	35–39	22	(11.5)	
	40–44	10	(3.9)	
	45–50	0	(0.0)	<0.001
Age group (years) for women with no live births	25–29	100	(84.8)	
	30–34	24	(55.8)	
	35–39	13	(44.8)	
	40–44	3	(9.7)	
	45–50	0	(0.0)	<0.001

For those women without a live birth, but planning to have children in the future, exactly half (63 of 126) planned to have their first child between the ages of 30–34 years. A further 37 (29.4%) planned to have their first child between ages 25–29 years. Fewer women (23, 18.3%) planned to have their first child when aged 34–39 years and only three (2.4%) women reported planning a first child at the age of 40 or more years. No women aged less than 30 years reported planning to have their first child when aged 35 years or more.

For those women without a live birth, but planning to have children in the future, almost two-thirds (82 of 129) reported that having children in the future was very important to them, 37 (28.7%) reported it was moderately important and 10 (7.8%) reported it was of little importance. For those women with at least one live birth and planning to have more children in the future, over a third (33 of 85)

reported that having children in the future was very important to them, 41 (48.2%) reported it was moderately important, 10 (11.8%) reported it was of little importance and one (1.2%) woman reported that it was of no importance.

Of women who completed the computerised questionnaire and reported they would like children in the future the vast majority (94.2%, 161 of 171) reported they would seek medical help if they experienced difficulties. Of these 161 women, 31 (19.3%) said they would try to conceive for less than six months before seeking help, 73 (45.3%) said they would wait 6–11 months, 51 (31.7%) said they would wait 1–2 years and 6 (3.7%) said they would try for more than two years before seeking help.

3.4.9 Knowledge and opinions

Fertility and infertility knowledge

All participants were briefly assessed on their knowledge using the five following multi-choice format questions (with the correct answers provided below each question):

- If a woman ovulates (produces an egg) on day 14 of her menstrual cycle, on which days is it possible to get pregnant?

  'Days 11–14'; if a woman ovulates on day 14 she is not fertile from day 14 until a few days before she next ovulates (Keulers *et al.*, 2007).

- At which age does women's fertility start to decline?

  '30 years'; fertility declines from age 30 on average, although more steeply from the mid-late thirties (Broekmans *et al.*, 2007).

- For women aged 30–35 years having regular intercourse without using methods to avoid pregnancy, what is the average chance of conception each month?

  '15–25%'; conception rates of 30% are seen in those aged 19–26 years, but his halves by the time women are 35–39 years (Taylor, 2003).

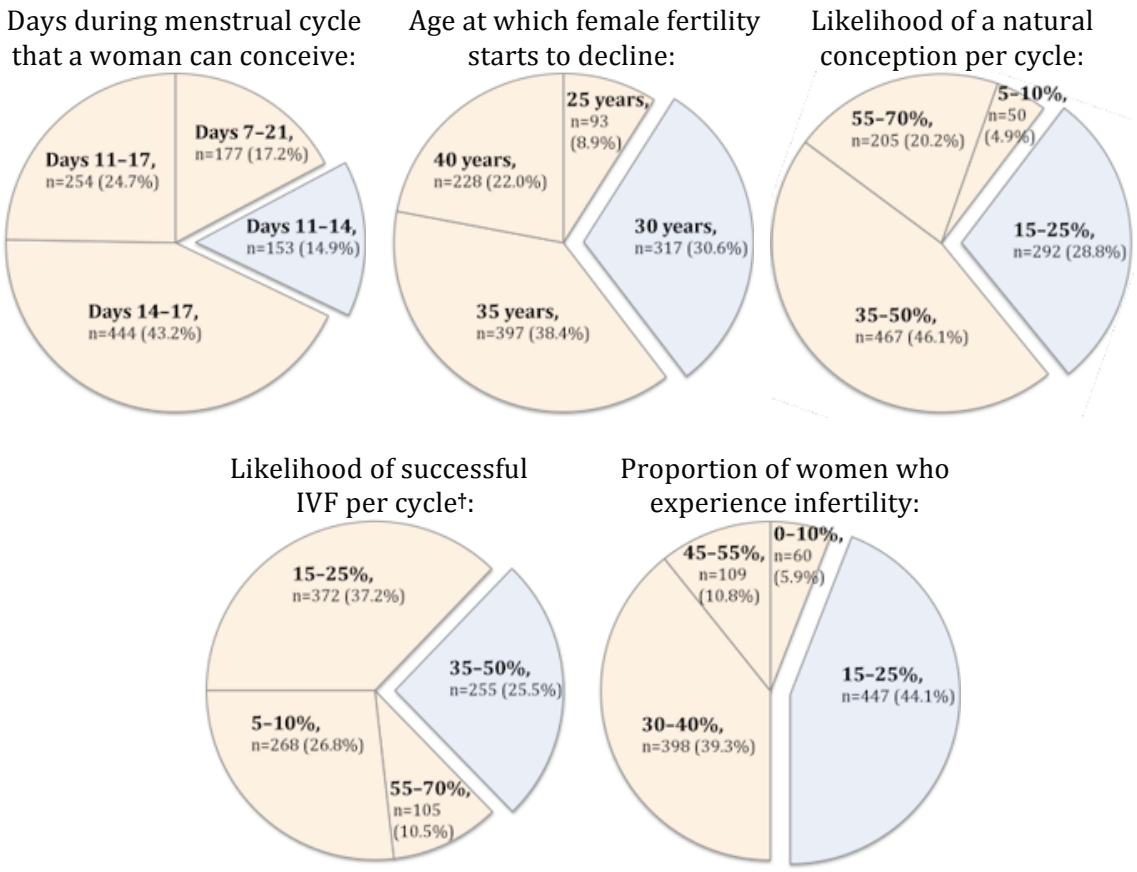
- For women aged 30–35 years having IVF (*In vitro* fertilisation), what is the average chance of conception resulting in a live birth after one treatment?

  '35–50%'; live birth rates of over 40% have been achieved after the implantation of all embryos collected from one IVF cycle (Advisory Committee on Assisted Reproductive Technology, 2014). However, following administering the questionnaire this question was found to be ambiguous and, as the live birth rate from a single implantation in New Zealand clinics was 33.5% for 30–34 year olds and 24.5% for 35–39 year olds in 2011, '15–25%' was also considered reasonable (and, therefore, correct for analysis of total correct responses).

- What percentage of all couples attempting to have children experience problems getting pregnant (infertility)?

  '15–25%'; estimates vary depending on how infertility is defined, but for 12 months or more trying to conceive estimates average at 19% for high-income countries (refer to Figure 2.2 on page 32) and a prevalence of one in six is commonly quoted in many articles, websites and magazines.

Figure 3.5 displays the numbers and proportions of women answering each response option and Figure 3.6 the total number of correct responses. The proportion answering each correctly was low, but more than that expected by chance (all $p<0.01$); however, for the question on fertile days in a menstrual cycle, the proportion answering correctly was even lower than that expected by chance ($p<0.001$). The responses to natural fertility questions were optimistic; 431 (41.9%) women believed that an average woman was fertile for six days or more during one menstrual cycle. Women commonly reported that fertility declines from age 35 years (397, 38.4%) and 228 (22.0%) believed that fertility does not start to decline until 40 years. Furthermore, 467, (46.1%) women reported that the likelihood of a conception occurring with regular unprotected intercourse was 35–50% per cycle. However, women had more realistic views of the likelihood of successful IVF and the proportion that experience infertility: 627 (62.7%) women reported the likelihood of successful IVF as being 15–25% or 35–50% and 447 (44.1%) correctly answering that 15–25% of women experience infertility.



* *The correct responses are shown in blue.*

† *Due to ambiguity in the question, for the likelihood of successful IVF '15–25%' was also considered an acceptable response.*

Figure 3.5: Distribution of responses to five fertility knowledge questions*

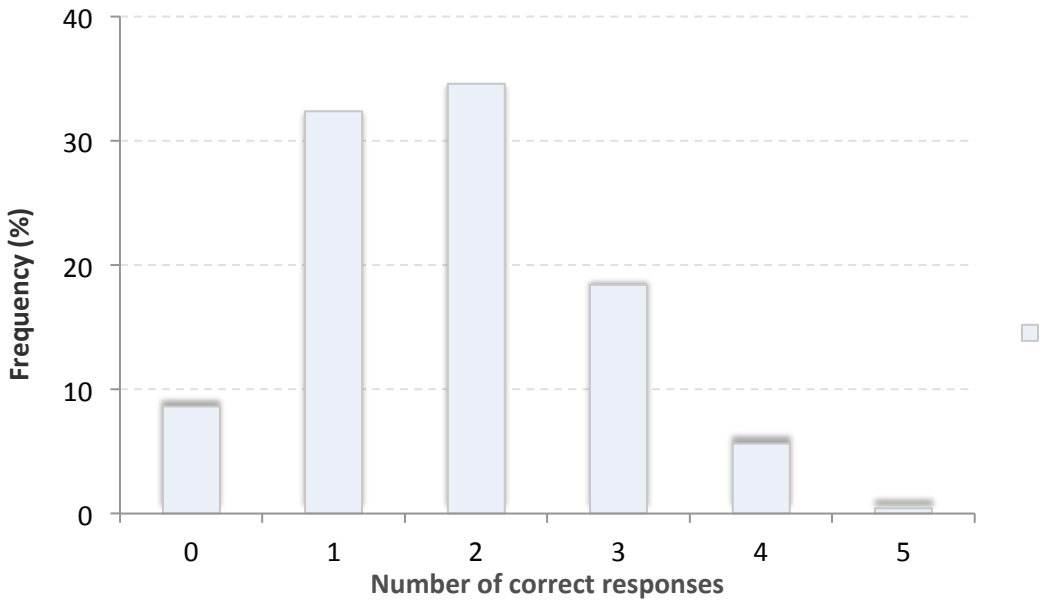


Figure 3.6: Frequency of total correct responses

Just four (0.4%) of the 974 women answering all questions answered them all correctly, which was not significantly different than would have been expected by chance (p=0.270). Most commonly, 337 (34.6%) women answered two questions and 315 (32.3%) answered one question correctly. The number of correct answers had a slight positive association with having experienced infertility (Pearson's χ^2 p=0.038), but there was no association with age group (Pearson's χ^2 p=0.954).

Ovulation monitoring behaviours

Almost a third of participants who answered questions on ovulation monitoring (325/1,034) reported using at least one method to monitor their ovulation. Women were much more likely to report having monitored their ovulation if they had ever tried for 12 months or more to conceive or needed medical help to conceive, with 129 (57.1%) doing so compared with 184 (27.8%) women without infertility (Pearson's χ^2 p<0.001). Women who monitored ovulation were more likely to report the correct answers for the fertile window knowledge question (18.4% compared with 13.1% in those who did not monitor ovulation, Pearson's χ^2 p=0.027), although knowledge was still poor.

The most commonly used method for ovulation monitoring was the calendar method (charting the date of their menstrual periods and counting days until expected ovulation), with 244 (23.6%) women reporting using this method. Of other common methods, 89 (8.6%) women used basal temperature monitoring (women's body temperature increases in the follicular phase of the menstrual cycle, peaking with ovulation), 54 (5.2%) used ovulation tests (typically these detect a surge in hormones that occurs immediately prior to ovulation) and 29 (2.8%) observed changes in their cervical mucus (mucus changes consistency and colour during the cycle and women can identify when they are fertile bases on having an 'egg white' like mucus). A further 16 (1.6%) women reported other methods such as 'physiological changes' and 'pain'.

Three-quarters (240 of 322, 74.5%) of women who monitored ovulation reported they did so in order to conceive. A quarter (80, 24.8%) reported doing so for contraception purposes and a quarter (79, 24.5%) for the purpose of learning

about their menstrual cycles. A further 17 (5.3%) reported other reasons such as 'for fun' and trying to optimise the likelihood of achieving the desired gender of their next child. A number of women indicate they had multiple reasons. Three women reported monitoring their ovulation but did not indicate their reason(s).

When women who monitored their ovulation were asked where they learned how to do this, a variety of sources were identified: Many women (106 of 321, 33.0%) sourced information from a non-specialist medical doctor; 88 (27.4%) from friends and/or family; 83 (25.9%) from the internet; 56 (17.5%) from books and/or magazines; 40 (12.5%) from a specialist medical provider; 25 (7.8%) from a non-medical health provider; and 13 (4.1%) women sourced information from their medical training. A further 19 women stated that they had used other sources of information. Other methods commonly mentioned were secondary school level education and 'research'. Four women reported monitoring their ovulation but did not indicate their information source(s).

Opinion about restriction of infertility treatment

All participants were asked their opinion about which factors should be used (if any) to limit women's/couple's access to publicly funded infertility treatment, given that there is not enough public funding for all women/couples experiencing infertility.

The list of possible restrictions from which women could select multiple responses and the respective numbers and proportions of women selecting each response are shown in Table 3.8 (overleaf). Over half of women thought that funding access should be restricted for women who were currently smoking or currently obese (62.3% and 53.0% respectively). Women also frequently responded that women who were not in a stable relationship should be restricted (39.2%), as well as those aged more than 40 years (30.5%) or less than 25 years (29.9%). Only 10.2% of women thought that couples with a child from a previous relationship should have restricted access.

Of the 1,032 women who responded to this question, 215 (20.8%) reported that access should not be limited by any factors. Two-thirds of women (696, 67.4%)

selected multiple restrictions, with almost a third (323, 31.3%) selecting four or more criteria on which to restrict. The number of restrictions selected was not associated with being infertile (having tried for 12 months or more or sought medical help to conceive) (Pearson's χ^2 p=0.829).

Table 3.8: Opinions about restriction criteria for accessing public funding for infertility treatment

Restriction criteria	Criteria selected n (%)
Aged less than 25 years old	309 (29.9)
Aged more than 40 years old	315 (30.5)
Currently a smoker	643 (62.3)
Currently obese (a BMI of 32kg/m^2 or more)	547 (53.0)
Not in a stable relationship	405 (39.2)
In a same-sex relationship	118 (11.4)
Already had children with current partner	205 (19.9)
Already had children with a previous partner	105 (10.2)
Total women responding to this question	1,032

3.4.10 Predictors of infertility

Associations between infertility (defined for this analysis as trying to conceive for 12 months or more or seeking medical help to conceive) and various demographic characteristics and known risk determinants for infertility were investigated using Poisson regression. The analysis was limited to women who had ever been pregnant or tried to conceive for 12 months or more.

Table 3.9 on page 118 shows the unadjusted and adjusted relative risks of infertility for selected demographic characteristics and other risk determinants.

Unadjusted analyses revealed statistically significant associations between infertility and relationship type, age and education (Wald test p=0.005, 0.017 and 0.036 respectively). Whilst Māori descent and household income were not

significantly associated with infertility, they warranted testing in a multivariate model, as the Wald test p-values for association with infertility were less than the 0.20 cut-off. BMI was significantly associated with infertility (Wald test p=0.019).

A multivariate model was built to simultaneously adjust for the selected (based on an unadjusted Wald test p-value of less than 0.20) demographic predictors and BMI. After starting with relationship type, the following variables were then added to the model stepwise (comparing the AICs to confirm any improvement in model fit): Age group; BMI; educational level; Māori descent; and household income. BMI remained significant after adding relationship type, education and household income to the model (these were the only variables that resulted in significant improvement to the model fit). Household income in itself was not significantly associated with infertility, but resulted in a significantly improved fit and appeared to have a slight confounding effect in masking the association between educational level and infertility, and thus remained in the model, with the results for this variable supressed.

After simultaneously adjusting for all variables as described, the relative risk of infertility was reduced (RR 0.50, 95% CI 0.28–0.90) amongst women who were single or in a same-sex relationship compared with women in a heterosexual relationship at the time of the survey. Women who were underweight were at 2.61 (95% CI 1.43–4.79) times the risk of infertility compared with women with a normal BMI. When also compared with normal BMI, women who were in the obese class II and class III categories were at 1.78 (95% CI 1.19–2.65) and 2.01 (95% CI 1.19–3.37) times the risk of infertility respectively. Women who had a university level qualification were at 1.19 (95% CI 1.04–1.35) times the risk of infertility compared with women without a university level qualification.

The final model was checked for internal validity using bootstrapping. All variables were still significantly associated with infertility (apart from household income) despite the wider confidence interval obtained from bootstrapping (data not shown).

Table 3.9: Unadjusted and adjusted relative risk of infertility* by selected demographic factors and risk determinants

		Number of women who experienced infertility (Prevalence, %)		Unadjusted†			Adjusted‡		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Demographic factors									
Relationship type	Heterosexual	216	(27.4)	Reference					
	Same-sex/no relationship	15	(13.6)	0.50	(0.31–0.81)	0.005	0.50	(0.28–0.90)	0.020
Age group (years)	25–29	19	(14.0)	0.52	(0.32–0.83)				
	30–34	38	(27.5)	1.02	(0.71–1.45)				
	35–39	53	(27.0)	Reference					
	40–44	79	(30.2)	1.12	(0.83–1.50)				
	45–50	57	(23.6)	0.87	(0.63–1.20)	0.017			
Māori descent	No	227	(25.9)	Reference					
	Yes	19	(19.2)	0.74	(0.49–1.13)	0.159			
Ethnic group	European	221	(25.9)	Reference					
	Māori	13	(18.8)	0.73	(0.44–1.20)				
	Other	6	(20.0)	0.77	(0.37–1.59)	0.373			
Educational level	Lower than university	148	(23.7)	Reference					
	University	80	(30.3)	1.13	(1.01–1.27)	0.036	1.19	(1.04–1.35)	0.010

Household income	Low (≤ $30,000)	17	(17.4)	0.65	(0.41–1.03)				
	Medium ($30,001–$70,000)	89	(26.1)	0.98	(0.78–1.24)				
	High (>$70,000)	112	(26.7)	Reference		0.179			
Deprivation (NZDep06)	Low (deciles 1–3)	116	(25.7)	Reference					
	Medium (deciles 4–7)	94	(25.9)	1.01	(0.80–1.28)				
	High (deciles 8–10)	36	(22.6)	0.88	(0.64–1.22)	0.714			
Other risk determinants									
Smoking status	Current smoker	36	(28.1)	1.04	(0.76–1.43)				
	Past smoker	65	(22.8)	0.85	(0.65–1.10)				
	Non-smoker	132	(26.9)	Reference		0.372			
BMI category, range (kg/m^2)	Underweight, <18.5	5	(55.6)	2.47	(1.34–4.55)		2.61	(1.43–4.79)	
	Normal, 18.5–24.9	91	(22.5)	Reference					
	Overweight, 25.0–29.9	54	(26.2)	1.16	(0.87–1.56)		1.19	(0.88–1.61)	
	Obese class I, 30.0–34.9	30	(25.2)	1.12	(0.78–1.60)		1.17	(0.80–1.69)	
	Obese class II, 35.0–39.9	23	(34.3)	1.52	(1.04–2.22)		1.78	(1.19–2.65)	
	Obese class III, ≥40.0	11	(36.7)	1.63	(0.98–2.70)	0.019	2.01	(1.19–3.37)	0.004

* *Infertility definition used: 12 months trying to conceive or sought medical help.*

† *All independent variables with an unadjusted p<0.20 were tested for inclusion in the adjusted model, but only those that improved the model fit (as assessed by a reduced AIC) remained in the model and were reported in the final model.*

‡ *Simultaneously adjusted for all variables reported in the adjusted analysis and for household income.*

The association between infertility and various procedures that may pose a risk to fertility and gynaecological conditions and were also investigated using Poisson regression. For the purpose of this analysis laparoscopy was removed from 'other operation below the abdomen as this technique is frequently used during infertility investigations.

Table 3.10 shows the unadjusted relative risks of infertility for these factors.

Table 3.10: Unadjusted relative risk of infertility* by selected procedures and diagnosed conditions

		Number of women who experienced infertility (Prevalence, %)		Unadjusted†		
				RR	(95 CI%)	P-value
Procedures						
Chemotherapy	No	228	(25.8)	Reference		
	Yes	3	(37.5)	1.45	(0.59–3.58)	0.417
Sterilisation	No	212	(26.3)	Reference		
	Yes	19	(22.1)	0.84	(0.55–1.27)	0.405
Operation on ovaries	No	213	(25.4)	Reference		
	Yes	18	(35.3)	1.39	(0.94–2.05)	0.096
Appendicectomy	No	208	(26.0)	Reference		
	Yes	23	(25.6)	0.98	(0.68–1.43)	0.933
Hysterectomy	No	214	(25.4)	Reference		
	Yes	17	(36.2)	1.43	(0.96–2.12)	0.080
Other operation below abdomen†	No	189	(25.4)	Reference		
	Yes	42	(28.8)	1.13	(0.85–1.51)	0.385
Diagnosed conditions						
PCOS	No	204	(24.2)	Reference		
	Yes	24	(53.3)	2.20	(1.63–2.97)	<0.001
PID	No	222	(25.4)	Reference		
	Yes	6	(46.2)	1.82	(1.00–3.31)	0.050
Endometriosis	No	196	(23.9)	Reference		
	Yes	32	(47.8)	2.00	(1.51–2.64)	<0.001

Table 3.10 *continued*		Number of women who experienced infertility (Prevalence, %)		Unadjusted†		
				RR	(95 CI%)	P-value
Fibroids	No	209	(25.0)	Reference		
	Yes	19	(38.0)	1.52	(1.05–2.21)	0.027
STI	No	192	(25.5)	Reference		
	Yes	36	(26.7)	1.04	(0.77–1.42)	0.780
Other gynaecological problem	No	190	(24.7)	Reference		
	Yes	38	(32.2)	1.30	(0.98–1.74)	0.145

* *Infertility definition used: 12 months trying to conceive or sought medical help.*

† *39 women who reported their 'other' operation was a laparoscopy were removed from 'other'.*

None of the procedures were found to significantly increase the risk of infertility. However, PCOS, PID, endometriosis and fibroids were all significantly associated with infertility. These associations could probably be partially explained by ascertainment biases due to infertility investigations; this is possibly evidenced by the fact that PID was significantly associated with infertility, but there was no association between infertility and STIs (the, usually, transient cause of PID, and as such would not be likely to be diagnosed in retrospect at an infertility clinic, whereas PID could be). Furthermore, it is possible some diagnoses become more salient for women who have experienced infertility, therefore, introducing recall bias. Hence, despite these conditions being known risk factors and strongly associated with infertility, they were not included in the multivariate modelling of infertility predictors.

3.4.11 Predictors of seeking primary health care for infertility

There were 235 women who had ever tried to conceive for at least 12 months or sought medical help to conceive, who also provided service seeking information. Of these women, 156 (66.4%) had sought primary health care for infertility.

Associations between seeking primary health care for infertility and various demographic characteristics and known risk determinants for infertility (which

may influence service seeking as they are linked to public funding access) were investigated using Poisson regression for these 235 women.

Table 3.11 shows the unadjusted relative risks of seeking primary health care for infertility for selected demographic characteristics and other risk determinants.

Table 3.11: Unadjusted relative risk of seeking primary health care for infertility* by selected demographic factors and risk determinants

		Number of women seeking services (Prevalence, %)		Unadjusted		
				RR	(95 CI%)	P-value
Demographic factors						
Relationship type	Heterosexual	148	(68.5)	Reference		
	Same-sex/No relationship	5	(33.3)	0.49	(0.24–1.00)	0.051
Age group (years)	25–29	13	(68.4)	0.98	(0.68–1.40)	
	30–34	25	(69.4)	0.99	(0.75–1.32)	
	35–39	35	(70.0)	Reference		
	40–44	49	(65.3)	0.93	(0.73–1.32)	
	45–50	35	(61.8)	0.88	(0.67–1.16)	0.909
Aged 35 years or more at onset	No	138	(69.0)	Reference		
	Yes	18	(51.4)	0.75	(0.53–1.04)	0.086
Māori descent	No	146	(66.4)	Reference		
	Yes	10	(66.7)	1.00	(0.69–1.46)	0.981
Ethnic group	European	138	(65.4)	Reference		
	Māori	8	(61.5)	0.94	(0.46–1.92)	
	Other	6	(100.0)	1.53	(0.68–3.46)	0.619
Educational level	Lower than university	91	(61.5)	Reference		
	University	60	(75.0)	1.10	(1.01–1.21)	0.031
Household income	Low (≤ $30,000)	9	(52.9)	0.72	(0.46–1.15)	
	Medium ($30,001–$70,000)	53	(59.6)	0.81	(0.66–1.00)	
	High (>$70,000)	82	(73.2)	Reference		0.076
Deprivation (NZDep06)	Low (deciles 1–3)	73	(65.8)	Reference		
	Medium (deciles 4–7)	62	(70.5)	1.07	(0.89–1.30)	
	High (deciles 8–10)	21	(58.3)	0.89	(0.65–1.21)	0.458

Table 3.11 *continued*		Number of women seeking services (Prevalence, %)		Unadjusted		
				RR	(95 CI%)	P-value
Other risk determinants						
Smoking status	Current smoker	18	(50.0)	0.72	(0.51–1.01)	
	Past smoker	44	(67.7)	0.97	(0.79–1.19)	
	Non-smoker	92	(69.7)	Reference		0.171
BMI category, range (kg/m^2)	Underweight, <18.5	3	(60.0)	0.91	(0.44–1.89)	
	Normal, 18.5–24.9	60	(65.9)	Reference		
	Overweight, 25.0–29.9	36	(66.7)	1.01	(0.80–1.29)	
	Obese class I, 30.0–34.9	21	(70.0)	1.06	(0.80–1.40)	
	Obese class II, 35.0–39.9	14	(60.9)	0.92	(0.64–1.32)	
	Obese class III, ≥40.0	4	(36.4)	0.55	(0.25–1.22)	0.737

* *Infertility definition used: 12 months trying to conceive or sought medical help.*

Seeking primary care for infertility was very common and educational level was the only factor significantly associated with this (Wald test p=0.031); those with a university level qualification were slightly more likely to seek primary health care than those without a university qualification.

Women who were currently not in a heterosexual relationship were half as likely to have sought primary health care compared with those in a heterosexual relationship, but this finding was not quite statistically significant (Wald test p=0.051).

Women with a higher household income were slightly more likely to seek primary care, as were women who were younger than 35 years when they first experienced infertility, however, these differences were also not significant (Wald test p=0.076 and 0.086 respectively).

These variables were all tested in a multivariate model, as their Wald test p-values were all less than 0.20 threshold. The only other variable that met inclusion criteria for testing in the multivariate model was smoking status.

A multivariate model was attempted by first adding educational level, followed by testing relationship type, household income and being aged 35 years or more at first infertility experience. The adjusted relationships were not significantly different to the unadjusted and educational level remained the only factor significantly associated with seeking primary care. Therefore, as there was only significant variable, it was not adjusted; the unadjusted risk of seeking care being 1.10 (95% CI 1.01–1.21) times greater for those with a university qualification.

3.4.12 Predictors of seeking specialist health care for infertility

Of the 235 infertile women for whom service seeking information was available, 114 (48.5%) women had sought specialist health care for infertility.

Associations between seeking specialist health care for infertility and various demographic characteristics and known risk determinants for infertility (which may influence service seeking as they are linked to public funding access) were investigated using Poisson regression for these 235 women.

Table 3.12 shows the unadjusted relative risks of seeking specialist health care for infertility for selected demographic characteristics and other risk determinants.

Table 3.12: Unadjusted relative risk of seeking specialist health care for infertility* by selected demographic factors and risk determinants

		Number of women seeking services (Prevalence, %)		Unadjusted		
				RR	(95 CI%)	P-value
Demographic factors						
Relationship type	Heterosexual	108	(50.0)	Reference		
	Same-sex/No relationship	4	(26.7)	0.53	(0.23–1.25)	0.148
Age group (years)	25–29	8	(42.1)	0.92	(0.50–1.68)	
	30–34	17	(47.2)	1.03	(0.65–1.62)	
	35–39	23	(46.0)	Reference		
	40–44	44	(58.7)	1.28	(0.89–1.82)	
	45–50	22	(40.0)	0.87	(0.56–1.35)	0.255

Table 3.12 *continued*		Number of women seeking services (Prevalence, %)		Unadjusted		
				RR	(95 CI%)	P-value
Aged 35 years or more at onset	No	101	(50.5)	Reference		
	Yes	13	(37.1)	0.74	(0.47–1.16)	0.184
Māori descent	No	107	(48.6)	Reference		
	Yes	7	(46.7)	0.96	(0.55–1.68)	0.885
Ethnic group	European	102	(48.3)	Reference		
	Māori	5	(38.5)	0.80	(0.39–1.61)	
	Other	3	(50.0)	1.03	(0.46–2.33)	0.812
Educational level	Lower than university	68	(46.0)	Reference		
	University	43	(53.8)	1.08	(0.95–1.24)	0.252
Household income	Low (≤ $30,000)	7	(41.2)	0.70	(0.39–1.26)	
	Medium ($30,001–$70,000)	35	(39.3)	0.67	(0.49–0.90)	
	High (>$70,000)	66	(58.9)	Reference		0.022
Deprivation (NZDep06)	Low (deciles 1–3)	52	(46.9)	Reference		
	Medium (deciles 4–7)	44	(50.0)	1.07	(0.80–1.42)	
	High (deciles 8–10)	18	(50.0)	1.07	(0.73–1.57)	0.891
Other risk determinants						
Smoking status	Current smoker	14	(38.9)	0.79	(0.51–1.23)	
	Past smoker	33	(50.8)	1.03	(0.77–1.39)	
	Non-smoker	65	(49.2)	Reference		0.527
BMI category, range (kg/m^2)	Underweight, <18.5	2	(40.0)	0.85	(0.28–2.54)	
	Normal, 18.5–24.9	43	(47.3)	Reference		
	Overweight, 25.0–29.9	28	(51.9)	1.10	(0.78–1.54)	
	Obese class I, 30.0–34.9	14	(46.7)	0.99	(0.64–1.53)	
	Obese class II, 35.0–39.9	10	(43.5)	0.92	(0.55–1.54)	
	Obese class III, ≥40.0	3	(27.3)	0.58	(0.21–1.56)	0.855

* *Infertility definition used: 12 months trying to conceive or sought medical help.*

Patterns of association were very similar to that seen for seeking primary health care for infertility, with women who were not in a heterosexual relationship being

half as likely to access specialist care compared with those in a heterosexual relationship, women aged 35 years or more at first infertility (compared with those who were younger) slightly less likely to access specialist care, as were current smokers (compared with non-smokers). However, none of these factors were significantly associated and smoking status was not included in testing for a multivariate model as its Wald test p-value was greater than 0.20. The only statistically significant determinant of seeking specialist infertility care was household income (Wald test p=0.022).

A multivariate model was attempted by first adding household income, followed by testing relationship type and being aged 35 years or more at first infertility experience. As with the previous service seeking model the relative risks were not significantly different to the unadjusted relationships; relationship type and age at first experience of infertility remained non-significant. Therefore, as household income level was the only significant variable, there were no adjusted results. The unadjusted estimates showed those in the low (RR 0.70, 95% CI 0.39–1.26) and medium (RR 0.67, 95% CI 0.39–1.26) categories were less likely to seek care compared with those in the high-income category.

3.4.13 Predictors of resolving infertility with a live birth

For the purpose of this analysis, only the resolution of a woman's first infertility experience was considered. Of the 235 women who were infertile (had tried for 12 months or more or sought medical help to conceive) and had provided information on resolution of infertility, 178 (75.7%) resolved their first episode of infertility with a live birth.

Table 3.13 on page 128 shows the unadjusted and adjusted relative risks of infertility resolution for selected demographic characteristics and other risk determinants.

Testing the possible predictor variables using Poisson regression revealed a statistically significant association for one variable; age at first infertility experience (Wald test p=0.032). Three further variables were considered for

testing in the multivariate model: Māori descent (Wald test $p<0.20$); age group at the time of completing survey (Wald test $p=0.208$, but significantly less women aged 25–29 years had resolved infertility compared with women aged 35–39 years); and deprivation ($p=0.210$, but an almost significant linear trend was detected using a χ^2 test for trend).

A multivariate model was built by first adding age at first infertility experience, then testing Māori descent, age group (when the survey was completed) and deprivation (as a linear term). Of these variables, age at first infertility experience remained significant and deprivation also improved the model fit and was statistically significant.

Adjusted findings showed that those aged 35 years or more were 29% less likely (RR 0.71, 95% CI 0.53–0.96) to resolve their infertility compared with those aged less than 35 years when they first experienced infertility.

Compared with being of low deprivation, there was an 11% decrease (RR 0.89, 95% CI 0.80–1.00) in infertility resolution for each category of higher deprivation, such that those in the highest deprivation deciles (deciles 8–10) were 22% less likely to resolve their infertility compared with those in the lowest deprivation deciles (deciles 1–3).

Table 3.13: Unadjusted and adjusted relative risk of resolving infertility* with a live birth by selected demographic factors and risk determinants

		Number of events (Prevalence, %)		Unadjusted†			Adjusted‡		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Demographic factors									
Relationship type	Heterosexual	164	(75.9)	Reference					
	Same-sex/No relationship	10	(66.7)	0.88	(0.61–1.27)	0.487			
Age group (years)	25–29	8	(42.1)	0.54	(0.31–0.93)				
	30–34	28	(77.8)	1.00	(0.79–1.25)				
	35–39	39	(78.0)	Reference					
	40–44	61	(81.3)	1.04	(0.87–1.25)				
	45–50	42	(76.4)	0.98	(0.79–1.21)	0.208			
Aged 35 years or more at onset	No	158	(79.0)	Reference					
	Yes	20	(57.1)	0.72	(0.54–0.97)	0.032	0.71	(0.53–0.96)	0.026
Māori descent	No	165	(75.0)	Reference					
	Yes	13	(86.7)	1.16	(0.93–1.43)	0.184			
Ethnic group	European	161	(76.3)	Reference					
	Māori	10	(76.9)	1.01	(0.74–1.37)				
	Other	3	(50.0)	0.66	(0.29–1.47)	0.588			

Educational level	Lower than university	113	(76.4)	Reference					
	University	58	(72.5)	0.97	(0.90–1.06)	0.532			
Income	Low (≤ $30,000)	13	(76.5)	1.00	(0.75–1.32)				
	Medium ($30,001–$70,000)	64	(71.9)	0.94	(0.79–1.10)				
	High (>$70,000)	86	(76.8)	Reference		0.731			
Deprivation (NZDep06)	Low (deciles 1–3)	89	(80.2)	Reference					
	Medium (deciles 4–7)	66	(75.0)	0.94	(0.80–1.09)				
	High (deciles 8–10)	23	(63.9)	0.80	(0.61–1.04)	0.210	0.89§	(0.80–1.00)	0.045
Other risk determinants									
Smoking status	Current smoker	26	(72.2)	0.93	(0.75–1.17)				
	Past smoker	48	(73.9)	0.96	(0.80–1.14)				
	Non-smoker	102	(77.3)	Reference		0.776			
BMI category, range (kg/m^2)	Underweight, <18.5	3	(60.0)	0.80	(0.39–1.66)				
	Normal, 18.5–24.9	68	(74.7)	Reference					
	Overweight, 25.0–29.9	44	(81.5)	1.09	(0.92–1.30)				
	Obese class I, 30.0–34.9	21	(70.0)	0.94	(0.72–1.22)				
	Obese class II, 35.0–39.9	19	(82.6)	1.11	(0.88–1.38)				
	Obese class III, ≥40.0	10	(90.9)	1.22	(0.97–1.52)	0.415			

Table 3.13 *continued*		Number of events (Prevalence, %)		Unadjusted†			Adjusted‡		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Service seeking									
Accessed primary care	No	38	(70.4)	Reference					
	Yes	105	(72.9)	1.04	(0.85–1.27)	0.728			
Accessed specialist care	No	68.2	(68.2)	Reference					
	Yes	80.0	(80.0)	1.17	(0.81–1.70)	0.403			

* *Infertility definition used: 12 months trying to conceive or sought medical help.*

† *All independent variables with an unadjusted p<0.20 were tested for inclusion in the adjusted model, but only those that improved the model fit (as assessed by a reduced AIC) remained in the model and were reported in the final model.*

‡ *Simultaneously adjusted for all variables reported in the adjusted analysis.*

§ *Deprivation group was added as a linear term in the adjusted model after confirming an unadjusted borderline significant χ^2 trend test.*

3.5 Discussion

3.5.1 Main findings

The prevalence of infertility

Of the study participants who had tried for or had a pregnancy, 21.7% (95% CI 19.1–24.4%) had ever tried unsuccessfully to conceive for at least 12 months. Just over half of these women, 12.8% (95% CI 10.7–15.2%) of all fertility-tested women, tried for at least 24 months to conceive on at least one occasion. The 12-month infertility estimates in this survey were slightly higher than for most other population-based studies of women in middle to high-income countries reviewed in Chapter Two. Estimates for 12 months trying to conceive ranged from 10.3–25.9% with a weighted average of just under 19% across comparable studies (refer to Figure 2.2 on page 32).

Including both those women who tried to conceive for 12 months or more and those who had sought medical help to conceive in the infertility definition gave an estimated prevalence of 25.3% (95% CI 22.6–28.1%) amongst women aged 25–50 years in Otago and Southland. A very similar estimate was found in a more recent cohort study amongst women aged 37–39 years who were born in 1972/3, in which the prevalence of trying to conceive for 12 months or longer or seeking medical assistance in this birth cohort was 26.0% (95% CI 21.8–30.6%) (van Roode *et al*., 2015). This cohort study's participants were born in Dunedin, the largest city in the Otago region. However, the results from this Dunedin-based cohort study may partly reflect infertility prevalence and risk outside of both Otago and even New Zealand as many of the cohort members no longer live in Dunedin. Nevertheless, this Dunedin cohort estimate compares very well with the subgroup of women aged 35–39 years in the current cross-sectional study, who had a prevalence of 27.0%.

When this definition of infertility was used in a study based in Scotland of women aged 31–50 years by Bhattacharya *et al.* (2009); they found a much lower proportion of 19.3% were infertile.

Nearly a quarter (22.5%, 95% CI 19.5–25.4%) of women reported that they felt they had had difficulty conceiving; there was significant (but not complete) overlap for women meeting the definition of infertility and self-defining as having had difficulty. A recent Australian survey by Marino *et al.* (2011) found a very similar proportion of women aged 28–30 years reporting difficulty conceiving (24.2% of the 607 participants who had ever sought a pregnancy).

Using the definition of 12 months or longer having regular intercourse without contraception yielded an infertility prevalence of 31.0% (95% CI 28.2–33.8%) amongst all participating women. This result is very similar to estimates from many other studies based in middle to high-income countries reviewed in Chapter Two, which varied from 22.8–33.8% (Webb and Holman, 1992, Gunnell and Ewings, 1994, Karmaus and Juul, 1999, Greil and McQuillan, 2004). This infertility definition does not take intention into account and, thus, may overestimate the burden of infertility. However, this definition still warrants consideration, as intent is not always simple to define and measure (Greil and McQuillan, 2010).

The experience of primary unresolved infertility amongst women aged 40 or more years, was similar to the only other estimates available (1.9% [95% CI 0.9–3.6%] compared with 2.2–2.4% in England) (Gunnell and Ewings, 1994, Buckett and Bentick, 1997, Oakley *et al.*, 2008).

Childlessness

Of participants who were aged over 40 years, 13.7% (95% CI 10.9–17.0%) were childless. The 2006 census showed that 16.7% of 40-year-old women were childless, this population prevalence of childlessness from the census falls within the confidence limits of the survey estimate.

Almost half of childlessness was involuntary; 6.7% of all study participants were involuntarily childless. This estimate is higher than seen in most other population-based surveys, where it was measured at just over four per cent (Schmidt *et al.*, 1995, Buckett and Bentick, 1997, Oakley *et al.*, 2008, Klemetti *et al.*, 2010). However, it is unknown whether these studies included social causes of infertility and involuntary childlessness (such as lack of a male partner, disabilities and

financial constraints) in their definition. In this survey, excluding the women who were likely to have been infecund due to social limitations from the definition of involuntary childlessness, reduced the estimate to 5.0%.

The involuntary childlessness measure lends support to the investigation of infertility amongst women who do not report intent to conceive: One in six involuntarily childless women reported having unprotected intercourse for more than 12 months without conceiving, but never reported intention to conceive and, yet, expressed a desire to have had children.

Service seeking, diagnoses and treatment for infertility

Overall, two-thirds of women who had ever tried to conceive for 12 months or longer or sought medical help to conceive had seen a non-specialist medical doctor regarding difficulties conceiving. Almost half of infertile women had sought the help of a specialist. Altogether 70.6% (95% CI 64.4–76.4%) of infertile women sought non-specialist and/or specialist care. Similarly, van Roode *et al*. (2015) reported that two-thirds of infertile women had sought medical help in their Dunedin-based cohort study.

In 20 studies from other middle to high-income countries, the proportion seeking help ranged from 35–89% (see Table 2.1 on page 37), but often the type of help sought was not defined, so this is difficult to compare with the survey data. The findings from the current study were very similar to the most recent studies in high-income countries of infertility amongst women who had or had tried to conceive. In Scotland, 67.1% of 46–50 year-old and 73.6% of 36–40 year-old infertile women had sought care (Bhattacharya *et al.,* 2009); and, in Australia, this was 71.7% of 28–33 year-old infertile women (Herbert *et al.,* 2009). Despite these similarities, due to differences in health care policies and provision, service uptake data from Australia and Scotland should be cautiously compared with that in New Zealand. In Australia, fertility treatment is partly or fully reimbursable without restrictions on age, number of treatment cycles or existing family size (Marino *et al*., 2011); this is not the case in New Zealand or Scotland (nor England), where access to publicly funded treatments is restricted (Human Fertilisation and

Embryology Authority, 2015, Gillett and Peek, 1997), and these differences presumably may affect women's decision making regarding attending infertility services.

The most common causes of infertility amongst women who had consulted a specialist were male factor (33.3%), ovulation disorder (24.6%) and unknown cause (23.7%). This was very similar to self-reported causes of infertility in Scotland, where ovulation disorders, sperm quality problems and unexplained were also the most common; each of these diagnoses accounted for approximately 30% of infertility for women with a diagnosis (Bhattacharya *et al.*, 2009).

Over a third of infertile women received infertility treatment. Of women who saw a specialist, the most common forms of treatment were drugs (50.5%) and IVF (39.3%). From self-reported information from population-based studies, the proportion of infertile women receiving treatment varied considerably from 9–33% (see Table 2.1 on page 37). However, often treatment was not explicitly defined or the definition varied in these studies, so this was again difficult to compare with the present study data.

Pathway for women's first experience of infertility

In order to examine care pathways and outcomes, a flow chart of women's first experience of infertility was constructed. First, despite meeting the definition of infertility, a small percentage (15.7%) of these women did not perceive they had difficulties conceiving. All of these women conceived after trying for 12 months or longer and three-quarters had a live birth from this conception. Of the women who did perceive that they had difficulties, less than a quarter did not seek care. Of these women who did not seek medical help, two-thirds had had a live birth on this attempt or a subsequent attempt, but the remaining third had primary unresolved infertility. Two-thirds of the women who consulted a non-specialist doctor also went on to see a specialist. Of those who had sought non-specialist help, but did not see a specialist, 89% eventually had a live birth and 10% had primary unresolved infertility. Over three-quarters of women who saw a specialist received

treatment. Of those who did not get treated, almost half remained infertile without resolution.

Resolution of women's first infertility experience in this study was quite high, with three-quarters of women resolving their first episode of infertility with a live birth. This is similar to the rate found by Buckett and Bentick (1997) in England, but higher than that found by Bhattacharya *et al.* (2009) in Scotland.

When looking across the pathway at resolution of the first episode of infertility, there were only 22 of 235 (9.4%) infertile women who had not sought specialist medical care that may have benefited from treatment, as they had not resolved their infertility. There were a further nine infecund women who sought specialist medical care, but had not received treatment, however, it may be that they were offered treatment but they decided against it due to costs, likelihood of success or another reason. As another 26 women received treatment but had not had a live birth, a total of 57 (24.3%) had not yet resolved infertility after their first episode.

Fertility expectations and desired family size

Almost four per cent of study participants were currently trying to conceive, 17.6% planned to have children in the future, 72.0% did not intend or could not have children in the future and a further 6.7% women were unsure.

For those women without a live birth, but planning to have children in the future, over three-quarters planned to have their first child before the age of 35 years. Just 18.3% planned to have their first child when aged 35–39 years and three women reported planning a first child at when aged of 40 or more years. However, intentions to start childbearing when fertility declines significantly, was very uncommon amongst younger participants; no women aged less than 30 years reported planning to have their first child when aged 35 years or more. For these women with future fertility intentions, a greater proportion of those without a live birth (almost two-thirds) reported that having children in the future was very important to them compared with women with at least one child (just over a third reported this). For all women reporting planning future children, 94.2% reported

they would seek medical help if they experienced difficulties, with more than half stating they would seek help before trying for 12 months.

Over a quarter of women aged 40 or more years with no plans to conceive in the future reported desiring more children than they had had. Women were more likely to report not having had any or as many children as desired if they had experienced infertility, or if they had no children or one child compared with women with two or more children. The concept of desired family size has some limitations, as it may not have been realistically attainable, or have been affected by external influences such as a partner's decisions or due to loss of a child. However, failure to achieve the desired number of children may also be due to increased time take to conceive a child.

Fertility knowledge

Of the five knowledge questions, 32.3% of women answered one question correctly and 34.6% answered two questions correctly. Just four (0.4%) women answered all questions correctly. The number of correct answers was not associated with being infertile or with age.

Women had a reasonably realistic view of the population experience of infertility, with 44.1% correctly stating that 15–25% of women experience infertility. However, responses to natural fertility questions were optimistic, with over a third of respondents believing that an average woman was fertile for six days or more during one menstrual cycle. Over a third of women reported that fertility declines from age 35 years and almost a quarter from 40 years of age. Furthermore, just under half of women reported that the likelihood of a conception occurring in a couple who are having regular unprotected intercourse was 35–50% per cycle. Conversely, women were more pessimistic about the likelihood of successful IVF treatment, with 64.0% women reporting this to be 25% or less per cycle.

Directly comparing this cross sectional study with other studies on fertility knowledge and attitudes is not possible as there have been few studies amongst varying populations, all using a variety of questions and questioning styles. However, similarly to other reviewed studies, most women overestimated both the

age at which fertility starts to decline and the likelihood of conception, and few women knew the likelihood of successful IVF treatment (refer to Section 2.8.1 on pages 58–61). However, a more recent study amongst US women showed that the majority of women were aware of negative consequences of aging, but the age at which women believed negative impacts started occurring was not asked (Lundsberg *et al*., 2014). Nevertheless, similar to the reviewed studies in Chapter Two and the current study, this recent US study and one further recent study amongst fertility patients in Canada (Swift and Liu, 2014), both concluded that overall knowledge was poor.

Ovulation monitoring behaviours

Ovulation monitoring was common; a third of study participants had monitored ovulation, the most common reason for this being to conceive. This behaviour was more likely in women who were infertile and was also associated with slightly better (but still poor) knowledge. Most women who monitored used the calendar method or basal temperature monitoring and had obtained information on methods from various sources, such as non-specialist medical providers, family and friends, books and the internet.

There is very little information available from other studies about how many women engage in ovulation monitoring, whether they do this correctly and interpret the results accurately. Only one other population-based study that measured the prevalence of ovulation monitoring was identified; Lundsberg *et al*. (2014) also found that around a third of participants had monitored their ovulation amongst a convenience sample of US women. As many women in this survey cited information sources such as family and friends, and overall women still had poor knowledge, this behaviour may not be of benefit to women trying to conceive and could be detrimental in some circumstances (e.g. if intercourse is delayed until the day women identify that they have ovulated).

Factors associated with the prevalence of infertility, service seeking and the resolution of infertility

The relative risk of infertility was independently associated with currently being in a heterosexual relationship, the risk was halved for women who were not in such a relationship (RR 0.50, 95% CI 0.28–0.90). Women who were underweight were at over twice the risk of infertility compared with women with a normal BMI (RR 2.61, 95% CI 1.43–4.79) and women who were in the obese class II and class III categories were at 1.78 (95% CI 1.19–2.65) and 2.01 (95% CI 1.19–3.37) times the risk of infertility respectively. The finding with BMI corresponds well with that of Hassan and Killick (2004), who found that being underweight was associated with a quadrupling and being in obese class II/III with a doubling of the time to pregnancy. Those with a university level education were at 1.19 (95% CI 1.04–1.35) times the risk of infertility compared with women without a university level education, this relationship was as expected for a high-income country (Callister and Didham, 2007, Terava *et al.*, 2008, van Roode, 2010).

Two factors were associated with service seeking amongst infertile women: Educational level and household income. Those who had a university level qualification were slightly more likely to seek non-specialist medical services than those without a university level qualification (RR 1.10, 95% CI 1.01–1.21). Those in the medium household income bracket were less likely to access specialist care than those in the high-income bracket (RR 0.67, 95% CI 0.49–0.90). Consultation with a GP is generally affordable for those on lower incomes in New Zealand; therefore, it is perhaps not surprising that seeking non-specialist care was not associated with household income. Specialist assessment for fertility was free of charge in the Otago and Southland regions (and without any eligibility criteria during the time of the study). However, there are likely to be other costs when seeking specialist care, such as time off work and travel costs, which may explain why those in the highest income bracket were more likely to seek specialist care. Similar associations have been found in other population-based studies in Finland and the USA (Terava *et al.*, 2008, Chandra and Stephen, 2010). In England social class was also found to be important, but the area-based measure of deprivation

available for this survey was not associated with service seeking. In New Zealand, age, BMI and smoking all impact on the likelihood of receiving publicly funded infertility treatment (partially as they influence the probability of a positive treatment outcome), yet these factors were not associated with seeking specialist infertility care. This suggests that non-specialist providers were not influenced by the probability of patients receiving publicly funded treatment and/or likely treatment success when referring women to specialist providers.

Resolution of first infertility experience was found to be associated with the age at which the first experience of infertility occurred and deprivation level. Those aged over 35 years when they first experienced infertility were less likely to resolve their infertility than those who were younger (RR 0.71, 95% CI 0.53–0.96) and those who were more highly deprived were also less likely to resolve their infertility, with an 11% decrease in resolution per increase in deprivation group (RR 0.89, 95% CI 0.80–1.00). Data from the Dunedin cohort study similarly found the resolution of infertility was less likely amongst women who experienced infertility at an older age (van Roode *et al*., 2015). No other population-based studies were reviewed that addressed the impact of an overall SES measure on resolution of infertility.

3.5.2 Study strengths and limitations

Strengths

This was a population-based study with a well-characterised sampling frame that had very good coverage in the age group included for this study. Basic demographic information was available for both the survey responders and non-responders. The use of a computer-based questionnaire minimised data coding and entry errors, standardised the way in which answers were elicited and possibly provided more complete disclosure of sensitive data. Another advantage of using a computerised questionnaire was that a comprehensive set of fertility questions could be asked, without presenting time consuming and complex questions to women for whom the questions did not apply. This comprehensive assessment uniquely allowed for the complete pathway from the first experience

of trying to conceive for 12 months or more (being infertile) through to various forms of services seeking and resolution of infertility at various stages to be examined.

Selection bias

Selection bias was introduced into the study estimates by two means: Inherent biases in the sampling frame; and differential response rates amongst the women randomly selected from the sampling frame. Those who were younger and those more deprived are less likely to be in the study's sampling frame (the electoral roll).

Of the randomly selected sample of women, only 60.1% of eligible women who were known or assumed to have received a study invitation participated. Those women who were aged 25–29 years were less likely to participate, as were those who were highly deprived and those of Māori descent. As these women had a lower prevalence of infertility (although not substantially so and statistically significant only for women aged 25–29 years), the overall prevalence of infertility could be overestimated. It is also likely that women may have participated differentially based on their fertility experiences, but the impact of this cannot be estimated as it is unknown whether infertile women would be more or less likely to participate.

However, despite the potential impact of selection bias, estimates for infertility are very similar to those published by van Roode *et al.* (2015), from a cohort study much less likely to influenced by selection bias due to their very low loss to follow up. Also, the estimated proportion of women who were childless was just slightly, but not significantly, lower than the New Zealand census data on childlessness.

Recall errors and measurement inaccuracies

It is unknown whether the recall of detailed fertility events is accurate; although results from methodological studies of fertility histories have suggested that recall of up to 20 years can be accurate (Baird *et al.*, 1991, Zielhuis *et al.*, 1992, Joffe *et al.*, 1995). It is also unknown as to whether the experience of infertility and resolution

of infertility impacts on recall differentially. This raises some questions, for example, was the experience of infertility as salient for women who resolved their infertility? Were fertility-related diagnoses as salient for women who had not experienced infertility? In van Roode *et al*.'s (2015) study not all women who reported in their fertility history that a pregnancy took longer than 12 months to conceive answered affirmatively to the question 'Have you ever tried for 12 months or longer to get pregnant, but it didn't happen?'. Furthermore, they found when asked about infertility experiences at two different ages, women who had reported infertility when younger did not report it again when assessed at an older age, suggesting that recall was not always accurate.

However, in this cross sectional study infertility was measured using both a fertility history method and using specific questions on infertility. Women not self-defining as having had difficulties conceiving, but who had taken longer than 12 months to conceive a pregnancy, were included as infertile. It is likely, however, that the experience of infertility may have been underestimated in women who did not have pregnancies and, therefore, did not report the amount of time it took to conceive.

Measurement inaccuracies were possible with regard to BMI as self-reported height and weight used to calculate this. It is expected that there were non-differential differences in the accuracy of the measurement instruments, however, it is also possible there was differential reporting of these measurements due to the social desirability of being taller and weighing less (Merrill and Richardson, 2009). If this occurred, it is possible that overall BMI was under-estimated in the participants. A recent Australian validity study found this was the case, but also concluded that there was still moderate to high agreement when BMI was calculated from web-based reports and that this method, therefore, provided acceptable accuracy (Pursey *et al*., 2014).

Ascertainment bias

Many of the procedures and conditions that impact on infertility, asked of all participants during the background section of the study questionnaire, could not

be meaningfully compared between infertile and non-infertile women. Almost three-quarters of women who experienced infertility sought medical care; these procedures (e.g. laparoscopies) and conditions (e.g. PCOS and PID) are commonly used/investigated during infertility care. Therefore, it is likely that the increased risk of infertility amongst women who have had these procedures/diagnoses is at least partially explained by increased opportunity for infertile women to have these procedures/investigations during infertility care.

Temporal association and reverse causation

As the study was of a cross-sectional design, important factors that influence infertility such as age, BMI and smoking were being ascertained either during the current experience of infertility or after the experience of infertility. It is unknown for BMI and smoking whether this measurement reflects their status prior to experiencing infertility. For BMI in particular reverse causation could be an issue; women may increase in BMI after having a child, therefore measuring BMI after having children may mask the effect of BMI on infertility and resolution of infertility.

3.5.3 Summary

The experience of infertility was common in this population-based survey of women aged 25–50 years. Amongst women who had tried to become or had been pregnant, 25.3% (95% CI 22.6–28.1%) had tried for at least 12 months or sought medical help to conceive. The robustness of this measure is called into question by the study's response rate of 60.1% and this being lower in sub-groups with a slightly lower prevalence of infertility, and that the infertility estimates from this study were slightly higher than in comparable studies in other high-income countries. However, the estimates of infertility from a Dunedin-based cohort study with very high retention rates and the measure of childlessness from the New Zealand census were both very similar to the survey results, therefore, suggesting that potentially the impact of selection bias may not have been severe.

Whilst the proportion of women who resolved their infertility with a live birth was high, with three-quarters resolving their first episode, a relatively high proportion of women over the age of 40 years were involuntarily childless (6.7%) or, overall, had fewer children than they desired (27.4%). Involuntary childlessness and having fewer children than desired were both strongly associated with having experienced infertility. Resolution of infertility was found to be negatively associated with being over 35 years old at first experience of infertility and with being more highly deprived. There was no association between being infertile and being deprived (although highly deprived women had slightly lower prevalence of infertility). Service access did not explain the lower rate of resolution amongst highly deprived women, as deprivation was not associated with accessing a non-specialist or a specialist medical provider.

There was a high rate of service access by infertile women and after accounting for women who had a live birth with or without accessing specialist care, less than 10% of infertile women may have benefited (by receiving advice and/or treatment to resolve their infertility) if they had accessed specialist infertility care. This suggests that in the Otago and Southland region, that specialist and, especially, non-specialist infertility care is both accessible and acceptable to the vast majority of women who have fertility concerns. However, it is uncertain whether these results can be generalised to other regions of New Zealand, as Otago and Southland have an overall less deprived population.

Overall, women were over optimistic about age–related fertility decline and the chances of natural conception per cycle. Yet, despite this over optimism, none of the participants aged 25–29 years intended to have their first child when aged 35 or more years. Whilst, amongst women aged 30 or more years, planning a first child at an older age was more common, this may not have been their intention when they were aged in their twenties. A third of women reported ovulation monitoring, most commonly for the purpose of conceiving. However, overall, fertility knowledge amongst women was poor, suggesting that potentially this monitoring was not being conducted or interpreted correctly by some of these women.

CHAPTER FOUR:

STUDY TWO: THE OTAGO FERTILITY SERVICE

Chapter Four outlines Study Two: An analysis of the OFS dataset. This includes background, objectives, methods, results and discussion. The literature regarding service use/provision, treatment and outcomes for infertility was previously detailed in Chapter two.

4.1 Background

The OFS is based in Dunedin Hospital, New Zealand. The OFS is the only source of specialised tertiary infertility care (which includes all infertility diagnostic and treatment services) for infertility in the Otago and Southland regions (which together are covered by the Southern DHB). Also, for the study period, the OFS provided the only source of specialised secondary infertility care (which includes infertility investigations and treatment by OI with clomiphene, but does not include any other treatment options) for the Otago region. The vast majority of secondary infertility care for Southland residents was also provided by the OFS. A full range of infertility diagnostic procedures, and both publicly and privately funded treatment services, are provided by the OFS.

In New Zealand, clinical priority access criteria (CPAC) are used in place of more traditional waiting lists to prioritise patients for publicly funded elective procedures (Hadorn and Holmes, 1997). CPAC tools are used to calculate a priority score for each patient; this score reflects their health need and ability to benefit from treatment. This process has suffered much criticism, particularly due to the regional variations in implementation and compliance of clinicians (MacCormick *et al.*, 2004, Derrett *et al.*, 2013). However, the CPAC system appears to be reasonably acceptable to the general population, and in evaluation has performed well for determining who would benefit most and was most in need of infertility treatment (Gillett, 2007, Oudhoff *et al.*, 2007). The infertility CPAC was first piloted at the OFS in 1998, before being fully implemented in New Zealand in 2000. This tool determines access to publicly funded ARTs (mostly IVF), IUI/DI and OI with

gonadotrophins. A separate gynaecology CPAC tool determines access to surgical treatments for infertility, with the exception of reversal of sterilisation.

As with other CPAC scoring systems, the infertility CPAC aims to prioritise patients who are most in need of treatment and are most likely to benefit from treatment (Gillett and Peek, 1997). For 'need', the infertility score primarily uses a 'social' score that considers the duration of infertility and whether the woman/couple already have a child. To identify 'benefit' two criteria are used, each being direct measures of the likelihood of live birth: The woman's age and the severity of any infertility diagnoses. A woman's BMI and smoking status also directly impact on eligibility. Women who smoke and/or who have a BMI outside of the range 18–32 kg/m^2 are not able to access publicly funded treatment until they cease smoking and/or their weight improves; this is due to the negative effect of smoking and an unhealthy BMI on the likelihood of conceiving a pregnancy.

To evaluate the infertility CPAC, the OFS maintained a detailed patient database from 1998–2005 (Gillett *et al.*, 2006, Gillett, 2007). Apart from the required CPAC information, the database also included information on the date of first assessment, patient diagnoses, any treatment(s), the date treatment(s) was initiated, the volume of both publicly and privately funded ARTs, patient outcomes and the discharge date from the service. Demographic and physiological indicators included date of birth, ethnicity, NHI number, relationship status, BMI and smoking status. This dataset is unique in New Zealand as all women attending the OFS had a CPAC assessment and their data were recorded, irrespective of whether they went on to receive treatment. Other centres in New Zealand have only recorded CPAC information for those women requesting publicly funded treatment.

The OFS dataset has been analysed and information from the dataset published previously, especially with respect to evaluation of the infertility CPAC tool (Gillett *et al.*, 2006, Gillett, 2007, Gillett *et al.*, 2012). The OFS dataset forms the basis of the analysis of service provision in Otago and Southland. The literature review for infertility service use data revealed a paucity of information on the coverage of services, patients' persistence in infertility programmes, overall determinants of receiving treatment and of infertility resolution (refer to Section 2.7.1, pages 45–

52). In New Zealand, descriptive information regarding infertility and infertility outcomes in both the population and clinical setting is lacking. The OFS dataset provides an opportunity to address these information gaps.

4.2 Study objectives

The analysis of OFS dataset addresses the third overall aim of this thesis, which was to:

Investigate service provision, causes of infertility and outcomes amongst women attending secondary and tertiary care for infertility in Otago and Southland (both overall and by selected demographic characteristics).

This aim was met by:

- Describing the numbers of women/couples attending the service between 1998 and 2005, by age, deprivation score and ethnicity.
- Describing the duration of infertility, diagnoses and severity, treatments and resolution of infertility amongst all women/couples for their first referral to the OFS.
- Building multivariate regression models to determine predictors of programme withdrawal, treatment access and successful resolution of infertility amongst infertility patients.

Comparison of these data with the prevalence study in Otago and Southland will assist in determining service coverage and accuracy of perceptions versus the reality of treatment access and success in Otago and Southland.

4.3 Methods

4.3.1 Data source and population

The OFS dataset contains a record for each episode of infertility for every woman/couple who attended the service from 1998–2005. In this period there were 1,436 new referrals. Of these, there were 27 patients referred from outside the Otago and Southland regions and, therefore, were excluded from analyses.

Follow up of the 1,436 patients concluded (for research purposes) at the end of 2010, at which time only 21 of these patients were still under active review. Each record has basic demographic information, duration of infertility at referral, smoking status and BMI. Detailed information is also recorded on diagnoses, their severity, any treatments undertaken and the outcome. The OFS is still the only tertiary provider of publicly or privately funded infertility care in the Southern DHB and provided secondary care for all but a few cases (some secondary cases were seen in Southland in the last two years on this study). Therefore, these data represent nearly all cases seen for infertility care in this region.

The Otago and Southland regional population size was sourced by request from Statistics New Zealand. The estimated resident female population aged 15–49 years for each year from 1998–2005, interpolated from the 1996, 2001 and 2006 census data, was used as the denominator data for calculation of annual incidence rates. The 2006 census population data estimates by age group, ethnicity and NZDep06 for Otago and Southland women aged 15–49 years were also sourced from Statistics New Zealand. Comparison population-based data on relationship status were sourced from the 472 female participants in a Dunedin-based birth cohort study when they were aged 32 years old, as detailed relationship data were not available at a regional or national level (Poulton *et al*., 2015).

4.3.2 Definition of primary and secondary infertility

The OFS recorded only those pregnancies ending in live birth and, as part of the CPAC social criteria, the number of previous live births (parity) was also recorded. Therefore, for the purpose of this analysis an adjusted definition was used for primary and secondary infertility. Primary infertility was defined as infertility with no previous live births and secondary infertility as infertility after at least one live birth.

4.3.3 Demographic and infertility risk information

Demographic information recorded in the OFS dataset included ethnicity and age. The dataset contained two variables that identified patients: Their name and their NHI number. The NHI number was only recorded for the female partner. The NHI

number is a unique number assigned to every person who has used health services in New Zealand. There is an index of information associated with each unique number, including residential address, date of birth, sex, and ethnicity (Ministry of Health, 2007). OFS patients' NHI numbers were mapped to the index information to provide prioritised ethnicity and the corresponding domicile area for their residential address and for each NHI number. The domicile codes were then linked to the domiciles' NZDep06 score in order to assign each patient an NZDep06 score. The NZDep06 score, an ecological measure of average neighbourhood SES, was used as a surrogate marker of individual SES (refer to Section 3.3.14, page 86, for detailed information on domicile areas and deprivation scores).

The OFS and NHI ethnicity records were compared and found to be 93.0% consistent (1,289/1,368) after excluding 41 missing ethnicity values from the NHI information (refer to Table 4.1). The main difference between these two records appeared to be under reporting of Māori ethnicity by the OFS, as these women were mainly recorded as European by the OFS.

Table 4.1: Comparison of ethnic groups recorded by the OFS and NHI

NHI prioritised ethnic group	Ethnic group recorded by the OFS					
	European	Māori	Pacific	Asian	Other	Total
European	1,183	4	0	1	25	1,213
Māori	30	51	2	0	1	84
Pacific	1	1	9	2	1	14
Asian	3	1	0	37	3	44
Other	2	0	1	1	9	13
Missing	33	0	1	1	6	41
Total	1,252	57	13	42	45	1,409

This difference is likely to be due to the prioritisation of the NHI ethnicity variable (refer to Section 3.3.13, page 84 for details on ethnicity prioritisation). OFS ethnicity information was used to fill in the 41 missing NHI ethnicity values. This

modified NHI-derived ethnicity variable was used for analyses to ensure consistency with the other studies in this thesis.

Age was derived using the patient's date of birth (as recorded by the OFS) and the date of their first appointment. Age was then categorised in five year age bands as follows: 15–19; 20–24; 25–29; 30–34; 35–39; 40–44; and 45–49 years.

The 2006 census counts of total resident population for the Otago/Southland DHB area by five-year age bands from 15–49 years, prioritised ethnicity and NZDep06 decile were obtained from Statistics New Zealand. These data were used to compare selected patient demographic information with the population demographics.

Two risk determinants for infertility, additional to age, were collected; smoking and BMI, which were both measured at the first appointment. Some data were missing for BMI because during the first year of the programme weight was not recorded. Following this smoking and BMI were carefully recorded for all cases as women who were currently smoking and/or outside of the BMI range of 18–32 kg/m^2 could not access public funding for ARTs until such time as they stopped smoking or improved their BMI. Smoking was self-defined by the patient as being a current smoker, which was confirmed verbally by their assessing clinician. BMI was calculated and then categorised according to World Health Organization (2014) guidelines as previously described in Section 3.3.15 on page 88.

4.3.4 Diagnosis categories, counts of diagnoses and severity scores

Diagnosis categories and severity classifications

The diagnostic categories recorded in the OFS dataset were: Ovulation disorder; endometriosis; tubal-peritoneal disorder; semen disorder in the male partner; other infertility (e.g. uterine fibroids); and unexplained infertility. Requests for reversal of sterilisation were considered as a severe tubal/peritoneal diagnosis for women or a severe semen disorder for men.

A score was derived to reflect the severity of each diagnosis with the hypothesis that the probability of spontaneous pregnancy will diminish with more severe

disease (Gillett *et al.*, 2012). The scores for each diagnostic category were based on the classification of endometriosis by the American Society for Reproductive Medicine (1997). A score of one was given for minimal, two for mild, three for moderate and six for severe (see Appendix H, page 343, for the CPAC scoring tool).

The severity score of unexplained infertility was based on the amount of time the couple had spent trying to conceive, and as such counted as a separate diagnosis for CPAC scoring purposes, even if it coexisted with another diagnosis. The unexplained category added a time dimension to the severity of other diagnostic types when calculating the combined diagnostic severity score (see below) (Gillett *et al.*, 2012). Thus, all women were given a score of at least one for unexplained infertility, irrespective of whether infertility investigations had been completed or other diagnoses had been made.

However, the routinely used definition of unexplained infertility is having no diagnosis after completed investigation. Therefore, for the purpose of calculating the prevalence of unexplained infertility, unexplained diagnosis was recoded to exclude cases with another diagnosis and cases with incomplete investigation and no diagnosis. This change did not affect the combined diagnostic severity score.

Counts of number of diagnoses

A variable was generated to count the number of diagnoses of any severity; a diagnosis was counted if scored as at least minimal. Another variable was generated to count the number of severe diagnoses of any severity; a diagnosis was, therefore, counted only if scored as severe. Both of these variables excluded unexplained infertility diagnoses from the count data.

Combined diagnostic severity score

For provision of publicly funded infertility services, a combined diagnostic severity score was calculated by adding the scores of the six diagnostic categories together (including a score of at least one for unexplained infertility irrespective of other diagnoses). This model recognised the importance of a combination of multiple

infertility factors counting towards the estimation of prognosis (Gillett *et al.*, 2012). The maximum possible score with all categories combined was 36.

This combined diagnostic score was then grouped and classified as follows:

- Minimal (a score of 1).
- Mild (a score of 2–3).
- Moderate (a score of 4–5).
- Severe (a score of 6–11).
- Very severe (a score of ≥12).

For women who did not qualify for public funding because of their smoking and/or BMI status, a combined severity score (and overall CPAC score) was still calculated. Those women who qualified for public funding were coded as such, but could not access this until such time as they ceased smoking and/or improved their BMI.

4.3.5 Treatment categories and treatment predominance

Whether or not patients qualified for public funding of treatment was recorded in the dataset. Those qualifying for surgery through the gynaecology CPAC were recorded separately. Qualification for public funding for ART/IUI treatment was determined by their infertility CPAC score, which for some patients changed during the course of their care with the OFS. These changes in the CPAC score occurred due to lengthening duration of infertility and/or changes in diagnosis severities. Therefore, these data were coded as either eligible within one year of enrolment, eligible after one year, or never eligible. Never eligible was further broken down to those aged less than 40 years and those aged 40 or more years.

The OFS recorded all intended treatments and summarised the predominant treatment that had been completed to an acceptable clinical standard. However, if a treatment was unsuccessful and the patient subsequently had another treatment that was of lower predominance, which was successful, then this successful treatment was considered the predominant treatment. The order of treatment predominance was IVF, followed by surgery, IUI/DI, OI and other.

Table 4.2 summarises the interventions included in these treatment categories.

Table 4.2: Interventions carried out at the OFS by treatment predominance category

Predominance category	Included interventions
IVF	IVF with own eggs and sperm, IVF with egg and/or sperm donation, IVF with preimplantation genetic diagnosis, use of frozen embryos and IVF with use of a surrogate.
Surgery	Ovarian surgery (including ovarian cystectomy, ovarian drilling), adhesiolysis, treatment of endometriosis by laparotomy or laparoscopy, salpingostomy, myomectomy, tubocornual anastomosis, reversal of sterilisation (male and female), hysteroscopic surgery and variocele surgery.
IUI/DI	IUI or DI with or without OI.
OI	Treatment with gonadotrophins, metformin or clomiphene, and luteal support.
Other	Referral to a dietician or other weight improvement interventions, counselling.

4.3.6 Data end points, resolution of infertility and duration of care

The coded end points in the OFS dataset were:

- Conceived with treatment.
- Conceived spontaneously.
- Treated, did not conceive.
- Decided against any treatment.
- In treatment.
- Withdrew.

'Deciding against treatment' was distinct from 'withdrawal' in that women/couples decided after consultation with their clinician not to proceed with treatment. Women/couples who withdrew may or may not have had treatment and fell into three categories: Withdrawal due to relationship separation; withdrawal due to moving away from the region; and loss of contact for unknown reasons.

In the context of the OFS dataset *conceived* refers only to pregnancies that ended in a live birth. Successful resolution of infertility was defined in this analysis as any

pregnancy during patient follow up that resulted in a live birth. Therefore, conception that resulted in a live birth, irrespective of treatment status, was considered as resolved infertility. Those who were treated without success, decided against treatment and did not spontaneously conceive, withdrew, or were still in treatment, were considered to be unresolved. Duration of care was measured in months from the referral date to last follow up (the end point of care).

4.3.7 Statistical description of the data

Data were limited to first referrals to the OFS for all analyses. Analyses followed the plan summarised in Figure 3.1 (refer to page 91).

First referrals were described by year of first appointment for that referral. The median age (in years) and duration of infertility (in months) at first referral were described over time. The annual incidence rate of infertility care was calculated by dividing the number of new referrals in the year by the estimated resident population of women aged 15–49 years in Otago and Southland for that year. Incidence rates were calculated per 100,000 women.

Frequencies of responses were calculated for relationship status, age group, ethnicity and deprivation score of the female patient. These frequencies (apart from relationship status) were compared with the distribution of these characteristics in the estimated resident population of women aged 15–49 years in Otago and Southland for 2006. For ethnicity, the findings using the NHI-derived variable were verified by running the same analysis with the OFS ethnicity variable.

Duration of infertility, diagnosis type, severity, number of concurrent diagnoses and overall diagnostic score were compared by infertility type. Predominant treatment, number of treatments, duration of treatment and treatment success were also compared by infertility type.

A priori hypotheses about relationships between predictor variables and the outcomes of particular interest (withdrawal from the programme, receiving treatment and resolving infertility) were included in a directed acyclic graph (refer

to Figure 4.1 on page 167) to aid in building the models (Greenland *et al.*, 1999, Glymour, 2006, Fleischer and Diez Roux, 2008, Westreich and Greenland, 2013).

All differences between categorical data, including relationships between predictor variables in the directed acyclic graph, were tested using Pearson's χ^2 test and, where there were ordered categorical variables, χ^2 tests for trend were performed. Continuous data were compared using two-sample Wilcoxon rank-sum tests. All analyses were conducted in STATA 12.1/SE.

4.3.8 Poisson regression modelling

The three outcomes, withdrawing from the infertility programme, access to treatment and resolution of infertility, were compared for all variables with direct and indirect relationships to the outcome (according to Figure 4.1 on page 167) using Poisson regression. Withdrawal from the programme for any reason was considered as withdrawal and having treatment was considered to be any ART, AI/DI, surgery or OI. Patients who received counselling, weight loss advice and referral were not considered to have received treatment. Resolution of infertility was defined as pregnancy resulting in a live birth. Those couples that separated (one of which was due to the death of their partner), and therefore withdrew from the programme, were considered as unresolved, as were all other women/couples without a recorded live birth.

As with regression analyses in the previous chapter, Poisson regression was chosen, as the odds ratios provided by logistic regression would overestimate the relative risk for common outcomes. The same method was employed as previously in Chapter Three; exposure time was not considered in the model and robust standard errors were applied.

Independent variables were screened for inclusion in the multivariate models based upon having a Wald test p-value of <0.20 in unadjusted analyses. For correlated measures (e.g. various measures of diagnoses), only the variable with the strongest association in unadjusted analyses was selected to avoid collinearity in the multivariate model.

In order to have at least 20 outcome events per covariate (and thereby avoid an overfit model), some categorical variables were collapsed to reduce the number of covariates to a maximum of 11 in the final model for withdrawal (as there 229 events, so this allows for 20 events per covariate), 44 for treatment (884 events) and 38 for infertility resolution (763 events).

AICs were used in a sequential model building strategy to determine which independent variables significantly improved the model. Bootstrapping was used to confirm the validity of the assumptions used to build the multivariate models. Each categorical parameter in each model was also checked for overall significance using Wald tests.

The unadjusted and adjusted RRs, as well as the 95% CIs and Wald test p-values were reported. For more detailed methods for the Poisson regression analyses used in this chapter, refer to Section 3.3.17, pages 90–92.

Resolution of infertility was further analysed, considering time to event and the effect of withdrawal from the OFS infertility programme due to a couple's separation as a competing risk for infertility resolution, using competing risk regression. This analysis was then compared with a Cox's proportional hazards regression to determine whether there was a strong effect of competing risk on resolution of infertility. For the methods and results table and figure for this analysis refer to Appendices J (page 349) and K (page 351) respectively.

4.4 Results

There were a total of 1,563 referrals over an eight-year period, with the first appointment date ranging from 05 January 1998–16 December 2005. These 1,563 referrals represented 1,482 women (and their partners, if applicable) and for 1,436 of these women this included their first ever referral to the OFS (some successfully treated women were referred for a second time in the same period). The data set was closed off at the end of 2010 by which time all but 21 couples had finished treatment. Of the 1,436 women, 1,409 were resident in Otago or

Southland when referred. Referrals were evenly spread during the eight years that the dataset was collected.

The analysis was restricted to the 1,409 first ever referrals who were resident in Otago or Southland. The annual incidence of first referral to infertility services in Otago and Southland varied over the eight-year time period from 208.4–280.1 referrals per 100,000 women aged 15–49 years. The median duration of infertility at presentation to the OFS varied little over time, ranging in duration from 24–26 months. The overall median duration for both primary infertility and secondary infertility was 24 months. The median duration of fertility care amongst these patients was 14 months.

4.4.1 Characteristics of patients presenting to the OFS

Table 4.3 shows the basic demographic characteristics of patients, compared with the 2006 resident population of women aged 15–49 years in Otago and Southland.

Table 4.3: Selected demographic characteristics of patients compared with the 2006 resident population of women aged 15–49 years in Otago and Southland

		Patients, n (%) N=1,409		Population, n (%) N=72,783*		P-value
Relationship status	Heterosexual	1,361	(96.6)	380*	(80.5)	
	Same-sex	21	(1.5)	4*	(0.8)	
	Not in a relationship	27	(1.9)	88*	(18.6)	<0.001
Age group (years)	15–19	6	(0.4)	11,442	(15.7)	
	20–24	78	(5.5)	11,475	(15.8)	
	25–29	325	(23.1)	8,310	(11.4)	
	30–34	495	(35.1)	9,474	(13.0)	
	35–39	372	(26.4)	10,179	(14.0)	
	40–44	118	(8.4)	11,118	(15.3)	
	45–49	15	(1.1)	10,785	(14.8)	<0.001
Ethnic group†	European and Other	1,265	(89.8)	61,989	(85.1)	
	Māori	84	(6.0)	6,210	(8.5)	
	Pacific	15	(1.1)	1,056	(1.5)	
	Asian	45	(3.2)	3,534	(4.9)	<0.001

Table 4.3 *continued*		Patients, n (%) N=1,409		Population, n (%) N=72,783		P-value
NZDep06 score	1 (least deprived)	257	(18.3)	7,356	(10.1)	
	2	151	(10.8)	7,539	(10.4)	
	3	168	(12.0)	8,361	(11.5)	
	4	147	(10.5)	8,067	(11.1)	
	5	148	(10.6)	7,668	(10.5)	
	6	135	(9.6)	7,245	(10.0)	
	7	154	(11.0)	7,407	(10.2)	
	8	149	(10.6)	8,319	(11.4)	
	9	76	(5.4)	8,592	(11.8)	
	10 (most deprived)	17	(1.2)	2,160	(3.0)	<0.001

* *Comparison data sourced from a population-based birth cohort study when participants were aged 32 years (N=472) (Poulton et al., 2015).*

† *Based on prioritised ethnic group recorded on the NHI with 41 missing values replaced by OFS data.*

The vast majority (96.6%) of women were in a heterosexual relationship, 27 (1.9%) were not in a relationship and 21 (1.5%) were in a same-sex relationship. Population data on relationship status, sourced from a local cohort study, were significantly different, with a much greater proportion of women not in a relationship ($p<0.001$).

Most (84.6%) of the women presenting at the clinic were aged 25–39 years. Overall, just over a third of women presenting for their first appointment were aged 35 years or more. From 1998–2005 there were increasing proportions of women aged 35 or more presenting for care (29.6% in 1998 vs. 39.5% in 2005), this was statistically significant (χ^2 test for trend $p=0.028$). This finding is unlikely to be explained by changes in the population structure; in this time period the proportion of women aged 35 and older in Otago and Southland increased slightly from 41.9% in 1998 to 44.2% in 2001, after which it was stable.

The majority of women were of European ethnicity (88.4%). There were 84 (6.0%) Māori women, 15 (1.1%) Pacific women, 45 (3.2%) Asian women, and 19 (1.4%) women of Other ethnicity. A significantly higher proportion of Māori compared

with non-Māori women presented with secondary infertility, 50.0% versus 31.1% respectively (Pearson's χ^2 p<0.001). This finding was replicated using the ethnicity recorded by the OFS. Women of both Māori and Other ethnicities were under represented compared with the population data (Pearson's χ^2 p<0.001).

Women who were referred to the clinic represented all deciles of deprivation. However, when compared with the deprivation distribution of the population, women who resided in the least deprived areas (deprivation decile 1) were over represented (18.3% of patients) and women residing in the areas with the highest levels of deprivation (deciles 9 and 10) were under represented (5.4% and 1.2% of patients respectively) (Pearson's χ^2 p<0.001).

4.4.2 Other determinants of Infertility risk

Table 4.4 shows the prevalence of smoking and distribution of BMI amongst patients by infertility type.

Table 4.4: New referrals by smoking status, BMI category and infertility type

	Primary infertility		Secondary infertility		Total	
	n	(%)	n	(%)	n	(%)
Smoker						
Yes	152	(15.9)	120	(26.4)	272	(19.3)
No	803	(84.1)	334	(73.6)	1,137	(80.7)
BMI category (in kg/m²)						
Underweight, <18.5	24	(2.6)	5	(1.2)	29	(2.2)
Normal, 18.5–24.9	557	(60.7)	220	(53.4)	777	(58.5)
Overweight, 25.0–29.9	163	(17.8)	82	(19.9)	245	(18.4)
Obese class I, 30.0–34.9	105	(11.5)	61	(14.8)	166	(12.5)
Obese class II, 35.0–39.9	32	(3.5)	28	(6.8)	60	(4.5)
Obese class III, ≥40.0	36	(3.9)	16	(3.9)	52	(3.9)
*Data missing**	*38*		*42*		*80*	
Total	955		454		1,409	

* *Missing category was excluded from percentages and statistical tests.*

Overall, 19.3% (272) women were current smokers at their first referral. Those presenting with secondary infertility were more likely to be smokers than those presenting with primary infertility (26.4 and 15.9% respectively, Pearson's χ^2 p<0.001).

Over half (58.5%) of women presented within the normal BMI range, with 18.4% being overweight, and a further 20.9% of women in the obese categories. Women with secondary infertility had a trend towards higher BMIs than women presenting with primary infertility (χ^2 test for trend p=0.003). Women presenting with primary infertility had a median BMI of 24.3, whereas those with secondary infertility had a median of 25.4 (two-sample Wilcoxon rank-sum p<0.001).

Overall, two-thirds of the 1,409 women (955, 67.8%) presented for their first referral with primary infertility (they had not previously had a live birth).

4.4.3 Diagnoses amongst infertility patients

Table 4.5 shows the diagnoses and diagnostic categories amongst patients by infertility type.

Table 4.5: New referrals by diagnosed causes and infertility type

Causes of infertility	Primary infertility, n (%)		Secondary infertility, n (%)		Total, n (%)	
Female factor						
Ovulation disorder	241	(25.2)	113	(24.9)	354	(25.1)
Endometriosis	228	(23.9)	53	(11.7)	281	(19.9)
Tubal/peritoneal	197	(20.6)	89	(19.6)	286	(20.3)
Sterilisation	3	(0.3)	49	(10.8)	52	(3.7)
Any female factor	524	(54.9)	257	(56.6)	781	(55.4)
Male factor						
Semen disorder	366	(38.3)	148	(32.6)	514	(36.5)
Sterilisation	26	(2.7)	14	(3.1)	40	(2.8)
Any male factor	392	(41.1)	162	(35.7)	554	(39.3)
Combined factor	149	(15.6)	57	(12.6)	206	(14.6)

Table 4.5 ***continued***

Causes of infertility	Primary infertility, n (%)	Secondary infertility, n (%)	Total, n (%)
Other			
Other cause	56 (5.9)	19 (4.2)	75 (5.3)
Unexplained infertility	145 (15.2)	65 (14.3)	210 (14.9)
Incomplete investigation and no diagnosis	21 (2.2)	19 (4.2)	40 (2.8)
Total patients	955	454	1,409

* *As women/couples may have more than one diagnosed cause for their infertility, percentages do not add up to 100%.*

Over half of women were diagnosed with female factor infertility, with little difference in this between primary and secondary infertility (54.9% and 56.6% respectively, Pearson's $\chi 2$ p=0.539). Amongst the female infertility diagnoses, ovulation disorders were most common (25.1% of women), again with little difference between primary and secondary infertility. However, endometriosis was twice as likely to be diagnosed amongst women with primary compared with secondary infertility (Pearson's χ^2 p<0.001).

Male factor infertility was slightly more common amongst those with primary infertility (41.1% compared with 35.7% in those with secondary infertility) and this bordered on statistical significance (Pearson's χ^2 p=0.054). Combined female and male factor infertility was experienced by 15.6% of patients with primary infertility and 12.6% of patients with secondary infertility. Other causes of infertility and unexplained infertility were diagnosed in 5.3% and 14.9% of patients respectively, yet again with little difference between primary and secondary infertility.

Incomplete investigation with the absence of a diagnosis was very uncommon (n=40, 2.8%). A quarter (10/40) of those with incomplete investigations were women who were in a same sex relationship or single. Twenty (50.0%) of the women who had no diagnosis had decided against treatment and a further 15

(37.5%) women had withdrawn before completing fertility investigations. Four women in heterosexual relationships conceived spontaneously before investigations were completed. One woman in a same-sex relationship failed treatment and did not have any diagnoses recorded.

Tables 4.6 and 4.7 show, by infertility type, the number of concurrent diagnoses of any severity and the number of concurrent severe diagnoses respectively. Excluding unexplained infertility as a diagnosis, 1,159 (82.3%) women/couples had at least one diagnosed cause for their infertility. There was a tendency for women with primary infertility to have more concurrent diagnoses than women with secondary infertility (Pearson's $\chi 2$ p=0.004). Just under half of women had one or more severe diagnoses; there was no significant difference for women with primary compared with secondary infertility (Pearson's χ^2 p=0.135).

Table 4.6: New referrals by number of diagnostic types* (of any severity) and infertility type

Number of diagnoses	Primary infertility, n (%)		Secondary infertility, n (%)		Total, n (%)	
None	166	(17.4)	84	(18.5)	250	(17.7)
One	513	(53.7)	272	(59.9)	785	(55.7)
Two	230	(24.1)	81	(17.8)	311	(22.1)
Three	40	(4.2)	17	(3.7)	57	(4.1)
Four	6	(0.6)	0	(0.0)	6	(0.4)
Total	955		454		1,409	

* *Count excludes unexplained infertility if there was another diagnosis.*

Table 4.7: New referrals by number of diagnostic types* (severe† only) and infertility type

Number of severe diagnoses	Primary infertility, n (%)		Secondary infertility, n (%)		Total, n (%)	
None	568	(59.5)	248	(54.6)	816	(57.9)
One	358	(37.5)	195	(43.0)	553	(39.3)
Two	27	(2.8)	11	(2.4)	38	(2.7)
Three	2	(0.2)	0	(0.0)	2	(0.1)
Total	955		454		1,409	

* *Count excludes severe unexplained infertility if there was another severe diagnosis.*

† *A 'severe' diagnosis is where one or more of the six diagnosis categories was given an individual severity score of 'six' (the highest score for a category).*

Table 4.8 shows the diagnostic score by infertility type.

Overall the distribution of diagnostic scores was different by infertility type (Pearson's χ^2 p=0.024); it appeared that this was driven by a higher proportion of women with secondary compared with primary infertility having very severe diagnostic scores. Thus, considering these diagnoses results in tandem, women with secondary infertility had fewer diagnoses than women with primary infertility, but their diagnoses tended to be of higher severity.

Table 4.8: New referrals by combined diagnostic score and infertility type

Combined diagnostic score	Primary infertility, n (%)		Secondary infertility, n (%)		Total, n (%)	
Minimal	120	(12.6)	55	(12.1)	175	(12.4)
Mild	89	(9.3)	31	(6.8)	120	(8.5)
Moderate	211	(22.1)	98	(21.6)	309	(21.9)
Severe	462	(48.4)	212	(46.7)	674	(47.8)
Very severe	73	(7.6)	58	(12.8)	131	(9.3)
Total	955		454		1,409	

* *The diagnostic score is calculated by combining the six individual diagnostic severity scores.*

4.4.4 Uptake of treatment

Table 4.9 shows the proportion of women who were eligible for publicly funded treatment by infertility type.

Table 4.9: New referrals by eligibility for public funding of treatment and infertility type

Public funding eligibility	Primary infertility, n (%)	Secondary infertility, n (%)	Total, n (%)
Eligible <1 year after referral	484 (50.7)	156 (34.4)	640 (45.4)
Eligible ≥1 year after referral	317 (33.2)	142 (31.3)	459 (32.6)
Never eligible and <40 years old	65 (6.8)	112 (24.7)	177 (12.6)
Never eligible and aged ≥40 years old	89 (9.3)	44 (9.7)	133 (9.4)
Total	955	454	1,409

Three-quarters of patients qualified through the infertility CPAC for publicly funded ARTs, although many (32.6%) were not eligible for at least a year after first attending the OFS. A significantly higher proportion of women with primary than secondary infertility were eligible for public funding within one year of their initial referral appointment (50.7% versus 34.4% respectively). Women with secondary infertility were overall much less likely to qualify for public funding during their care (Pearson's χ^2 $p<0.001$).

Table 4.10 shows the predominant treatment received by infertility type.

Just under two-thirds of women had some form of treatment, and one-third of women received at least one round of IVF. The proportion of women receiving IVF was much greater for those with primary infertility, and the proportion that did not have any treatment was greater for women with secondary infertility (Pearson's χ^2 $p<0.001$). Just over one-third of women/couples did not undergo any form of intervention for their infertility.

Table 4.10: New referrals by predominant treatment and infertility type

Predominant treatment	Primary infertility, n (%)		Secondary infertility, n (%)		Total, n (%)	
IVF	390	(40.8)	97	(21.4)	487	(34.6)
Surgery	68	(7.1)	51	(11.2)	119	(8.5)
IUI/DI	97	(10.2)	36	(7.9)	133	(9.4)
OI	80	(8.4)	64	(14.1)	144	(10.2)
Other	32	(3.4)	13	(2.9)	45	(3.2)
No treatment*	288	(30.2)	193	(42.5)	481	(34.1)
Total	955		454		1,409	

* *Whilst no major treatment was undertaken, women were provided with supportive management as appropriate, e.g. advice on weight loss, smoking cessation and fertility.*

4.4.5 Care end points

Table 4.11 shows the last recorded outcome at the end of care with the OFS by infertility type.

Table 4.11: New referrals by outcome and infertility type

Care end points	Primary infertility, n (%)		Secondary infertility, n (%)		Total, n (%)	
Conceived* with treatment	330	(34.6)	146	(32.2)	476	(33.8)
Conceived* spontaneously†	203	(21.3)	84	(18.5)	287	(20.4)
Treated, but did not conceive*	169	(17.7)	67	(14.8)	236	(16.8)
Decided against treatment	82	(8.6)	78	(17.2)	160	(11.4)
In treatment	18	(1.9)	3	(0.7)	21	(1.5)
Withdrew	153	(16.0)	76	(16.7)	229	(16.3)
Total	955		454		1,409	

* *Conceived refers only to pregnancy ending in a live birth, pregnancies with other outcomes were not recorded.*

† *This may partially reflect a benefit of health sector supportive management even though the conception did not arise from treatment directly.*

Of the 1,409 women/couples who attended the clinic from 1998–2005 for their first referral, for 763 (54.2%) the endpoint of follow up for their referral was a pregnancy resulting in live birth. A further 16.8% of patients had unsuccessful treatment, and the remaining women/couples withdrew, decided against treatment, or were still in treatment when the data were last updated. Significantly more women with primary than secondary infertility conceived (55.9% versus 50.7% respectively), although women with primary infertility also had more unsuccessful treatments (Pearson's χ^2 $p<0.001$). Women with secondary infertility were more likely to choose not to have treatment than women with primary infertility.

4.4.6 Proposed relationship between demographic, risk and diagnostic factors and outcomes: Treatment access, programme withdrawal and resolution of infertility

Following the description of the patients and their demographic characteristics, risk determinants, diagnoses and treatment, the relationship between these factors and the outcomes of particular interest were examined. Figure 4.1 shows a directed acyclic graph of the *a priori* proposed relationships between the hypothesised predictors and the outcomes of interest: Withdrawal from the infertility programme; receiving treatment; and infertility resolution. Due to the complexity of this directed acyclic graph, each relationship has been numbered. This arrow reference number, the proposed relationship, and the Pearson's χ^2 test for a statistically significant difference between the variables (measures) as indicated in Figure 4.1 are reported in Appendix I from page 345. To avoid further complexity, this figure does not include other hypothesized pathways that could not be explored using OFS data (as these data were not collected). For example the relationship between level of anxiety and infertility resolution and the role of non-treatment support such as improving knowledge were not included.

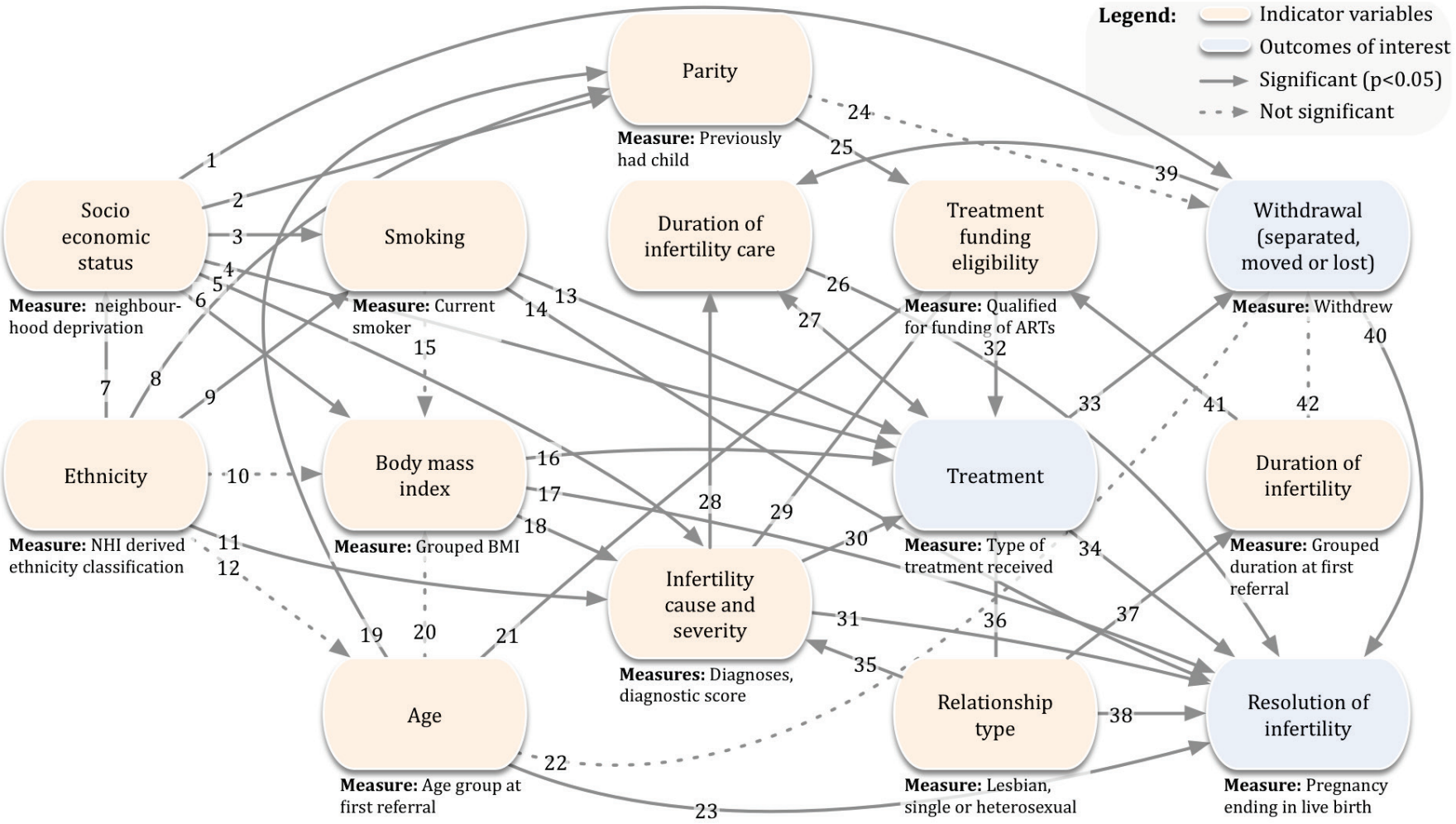


Figure 4.1: Proposed pathways between predictors, and from these predictors to outcomes of interest (withdrawal from programme, treatment and resolution of infertility)

4.4.7 Predictors of withdrawal from the infertility programme

Of the 229 women/couples who withdrew from the programme, 48 (21.0%) had separated, 65 (28.4%) had moved away from the Otago and Southland regions and a further 116 (50.7%) were lost for unknown reasons (no further contact could be made with these patients).

The median duration of care varied significantly depending on the reason for withdrawal, being 14, 11 and 6 months for separated, moved and lost respectively. The difference in duration in care between those who moved or separated and those who were lost was statistically significant (two-sample Wilcoxon rank-sum $p=0.041$ and $p=0.002$ respectively). As expected the duration of care for those who withdrew was also significantly less than for those who did not withdraw from the programme.

Table 4.12 on page 170 shows the unadjusted and adjusted relative risks of withdrawal from the programme by selected demographic characteristics, other risk determinants, diagnoses, funding eligibility and treatment type.

Unadjusted regression analysis showed that deprivation score, ethnicity, BMI, smoking and predominant treatment received were all highly associated with withdrawal from the infertility programme (Wald tests all $p<0.01$). A multivariate model was built to adjust simultaneously for all of these predictors, by first adding deprivation, then stepwise (comparing the AICs to confirm any improvement in model fit), ethnicity, BMI and smoking. These all resulted in significant improvement to the model fit. Relationship type, diagnostic score, severe ovulation disorder, number of severe diagnoses were then each fitted and compared (as these had Wald tests of $p<0.20$), but none of these variables contributed to a significant improvement in the model. Therefore the final model included deprivation, ethnicity, smoking status and BMI.

After adjusting for ethnicity, smoking and BMI, those in the highest deprivation group were almost 70% more likely to withdraw compared with those in the lowest deprivation group (RR 1.67, 95% CI 1.18–2.34). Given the high relative risk and significance of this adjusted estimate, the association between higher

deprivation and increased risk of withdrawal is only partially explained by those in the higher deprivation group having increased rates of smoking and higher BMIs (that then disqualify them from treatment, and hence a possible reason for their withdrawal). An elevated risk of withdrawal amongst Māori women/couples compared with European (RR 1.55, 95% CI 1.03–2.32) was confirmed. Those risk determinants that are linked to funding access were also still associated with withdrawal after adjusting; amongst smokers the relative risk was 1.44 (95% CI 1.09–1.92) compared with non-smokers and amongst those in BMI classes Obese II and III the relative risk was 1.83 (95% CI 1.17–2.87) and 2.04 (95% CI 1.32–3.18) respectively compared with a normal BMI.

Treatment was not considered for the final adjusted model as it was on the causal pathway between these potential modifiable risk determinants and withdrawal (refer to Figure 4.1 on page 167). When treatment was added to the final model, there was no longer any association between smoking or BMI and withdrawal, confirming that lack of access to treatment was probably the reason why those with high BMIs and/or who smoke withdrew from the programme. Adding treatment to the model did not affect the relationship between deprivation and withdrawal (data not shown).

The final model was checked for internal validity using bootstrapping. All variables were still significantly associated with withdrawal despite the wider confidence interval obtained from bootstrapping (data not shown).

Table 4.12: Unadjusted and adjusted relative risk of withdrawal by demographic factors, other risk determinants, duration of infertility, diagnoses, funding eligibility and treatment type

		Number of withdrawals (Prevalence, %)		Unadjusted*			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Demographic factors									
Parity	0	153	(16.0)	Reference					
	≥1	76	(16.7)	1.04	(0.81–1.34)	0.732			
Relationship type	Heterosexual	217	(15.9)	Reference					
	Same-sex/no relationship	12	(25.0)	1.57	(0.95–2.60)	0.081			
Age group (years)	<30	71	(17.4)	1.10	(0.82–1.48)				
	30–34	78	(15.8)	Reference					
	35–39	59	(15.9)	1.01	(0.74–1.37)				
	≥40	21	(15.8)	1.00	(0.64–1.56)	0.914			
Ethnic group	European	187	(15.0)	Reference					
	Māori	24	(28.6)	1.90	(1.32–2.74)		1.55	(1.03–2.32)	
	Other	18	(22.8)	1.52	(0.99–2.33)	<0.001	1.49	(0.92–1.92)	0.041
Deprivation	Low (deciles 1–3)	72	(12.5)	Reference					
	Medium (deciles 4–7)	91	(15.6)	1.25	(0.94–1.66)		1.16	(0.87–1.57)	
	High (deciles 8–10)	64	(26.5)	2.12	(1.57–2.86)	<0.001	1.67	(1.18–2.34)	0.012

Other risk determinants									
Current smoker	No	165	(14.5)	Reference					
	Yes	64	(23.5)	1.62	(1.25–2.10)	<0.001	1.44	(1.09–1.92)	0.012
BMI category, range (kg/m^2)	Underweight, <18.5	6	(20.7)	1.49	(0.71–3.10)		1.42	(0.71–2.81)	
	Normal, 18.5–24.9	108	(13.9)	Reference					
	Overweight, 25.0–29.9	31	(12.7)	0.91	(0.63–1.32)		0.88	(0.61–1.28)	
	Obese class I, 30.0–34.9	28	(16.9)	1.21	(0.83–1.78)		1.14	(0.78–1.67)	
	Obese class II, 35.0–39.9	17	(28.3)	2.04	(1.31–3.16)		1.83	(1.17–2.87)	
	Obese class III, ≥40.0	18	(34.6)	2.49	(1.65–3.76)	<0.001	2.04	(1.32–3.18)	0.004
Diagnostic variables									
Duration of infertility (years)	<2	91	(15.2)	Reference					
	2–4	86	(17.7)	1.17	(0.89–1.53)				
	>4	41	(17.5)	1.15	(0.82–1.61)	0.494			
Severe tubal/ peritoneal disorder	No	193	(15.8)	Reference					
	Yes	36	(19.0)	1.20	(0.87–1.65)	0.274			
Severe endometriosis	No	225	(16.4)	Reference					
	Yes	4	(11.8)	0.72	(0.28–1.82)	0.486			
Severe ovulation disorder	No	211	(15.9)	Reference					
	Yes	18	(23.1)	1.46	(0.95–2.22)	0.083			

Table 4.12 continued		Number of withdrawals (Prevalence, %)		Unadjusted*			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Severe semen disorder	No	183	(16.6)	Reference					
	Yes	46	(15.1)	0.91	(0.68–1.23)	0.552			
Severe other infertility	No	223	(16.2)	Reference					
	Yes	6	(20.7)	1.28	(0.62–2.64)	0.503			
Severe unexplained infertility	No	194	(15.9)	Reference					
	Yes	35	(18.7)	1.18	(0.85–1.63)	0.322			
Number of severe diagnoses	0	131	(16.1)	Reference					
	1	87	(15.7)	0.98	(0.76–1.26)				
	≥2	11	(27.5)	1.71	(1.01–2.90)	0.117			
Number of diagnoses	<2	166	(16.0)	Reference					
	≥2	63	(16.8)	1.05	(0.81–1.37)	0.717			
Combined diagnostic score	Minimal	24	(13.7)	Reference					
	Mild	25	(20.8)	1.52	(0.91–2.53)				
	Moderate	52	(16.8)	1.23	(0.78–1.92)				
	Severe	99	(14.7)	1.07	(0.71–1.62)				
	Very severe	29	(22.1)	1.61	(0.99–2.64)	0.113			

Treatment variables						
Qualified for public funding	No	49	(15.8)	Reference		
	Yes	180	(16.4)	1.04	(0.78–1.38)	0.810
Predominant treatment	None	112	(23.3)	Reference		
	IVF	38	(7.8)	0.34	(0.24–0.47)	
	Surgery	22	(18.5)	0.79	(0.53–1.20)	
	IUI/DI	12	(9.0)	0.39	(0.22–0.68)	
	OI	23	(16.0)	0.69	(0.46–1.03)	
	Other	22	(48.9)	2.10	(1.49–2.95)	<0.001

* *All independent variables with an unadjusted p<0.20 were tested for inclusion in the adjusted model, but only those that improved the model fit (as assessed by a reduced AIC) remained in the model and were reported in the final model.*

† *Simultaneously adjusted for all variables reported in the adjusted analysis.*

4.4.8 Predictors of receiving treatment

Almost two-thirds (884/1,409) of patients received some form of treatment, being ARTs, surgery, IUI, DI and/or OI.

Table 4.13 on page 176 shows the unadjusted and adjusted relative risks of receiving treatment by selected demographic characteristics, other risk determinants, diagnoses and funding eligibility.

The unadjusted regression analyses showed the demographic factors associated with a decreased likelihood of treatment were having children, being aged 40 years and over compared with age 30–34 years, and being in the medium or high deprivation groups compared with the low deprivation group (Wald tests all $p<0.05$). Māori women/couples also had significantly decreased treatment levels compared with European ethnicity (Wald test $p=0.020$). Smoking and having a BMI of 35 kg/m^2 or more compared with the normal weight category were both significantly associated with a reduction in treatment (Wald tests both $p<0.01$). Of the individual severe diagnoses, severe endometriosis, severe semen disorder and severe unexplained infertility were significantly associated with receiving treatment (Wald tests all $p<0.05$). Increasing level of treatment was highly associated with having two or more diagnoses (compared with none or one), one severe diagnosis (but not two severe diagnoses) compared with none, and with overall increasing diagnostic score (Wald tests all $p<0.001$). Receiving funding was also significantly associated with an increase in treatment level (Wald test $p<0.001$). Of all of these associations, there were only two strong associations: Having a BMI of over 40kg/m^2 compared with normal body weight (RR 0.41, 95% CI 0.26–0.65); and having a diagnostic score of at least moderate compared with minimal (RR 2.12, 95% CI 1.66–2.69).

A multivariate model was built to simultaneously adjust for all of these predictors, by starting with the demographic predictors: parity, then stepwise (comparing the AICs to confirm any improvement in model fit) deprivation, age and ethnicity. Of these, deprivation and ethnicity did not contribute to a significant improvement in the model fit. Following this BMI and smoking were added, both of which were

significant. While a number of diagnostic variables met the $p<0.20$ criteria for being fitted and tested in the model, due to colinearity issues, only diagnostic score was added (as it is a summary of number of diagnoses and severity of these diagnoses); diagnostic score contributed significantly to the model fit. Then ethnicity and relationship type were both fitted and compared, but neither of these variables contributed to a significant improvement in the model. Finally treatment funding was added, but this did not contribute to the model, and in fact the RR was reduced to almost one. This suggests that the crude association between funding and treatment was a consequence of funding being on the causal pathways from parity, age and diagnostic score to treatment (as predicted in Figure 4.1 on page 167).

The final model, which included parity, age group, smoking, BMI and diagnostic score, was checked for internal validity using bootstrapping rather than robust standard errors. All variables in the final model were still significantly associated with receiving treatment despite the slightly wider confidence interval obtained from bootstrapping (data not shown).

There was very little difference in the relative risks between the unadjusted and adjusted analyses for those variables included in the final model, suggesting there was little confounding. Therefore, there were two variables that had strong associations after adjusting for multiple factors: Having a BMI 40kg/m^2 or more compared with normal weight was strongly associated with a reduced likelihood of treatment; and having a diagnostic score that was more than minimal compared with minimal was strongly associated with an increased likelihood of treatment.

Table 4.13: Unadjusted and adjusted relative risk of receiving treatment by demographic factors, other risk determinants, duration of infertility, diagnoses and funding eligibility

		Number of patients receiving treatment (Prevalence %)		Unadjusted*			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Demographic factors									
Parity	0	636	(66.6)	Reference					
	≥1	248	(54.6)	0.82	(0.75–0.90)	<0.001	0.83	(0.75–0.91)	<0.001
Relationship type	Heterosexual	855	(62.8)	Reference					
	Same-sex/no relationship	29	(60.4)	0.96	(0.76–1.21)	0.742			
Age group (years)	<30	256	(62.6)	0.94	(0.86–1.04)		0.92	(0.84–1.01)	
	30–34	328	(66.3)	Reference					
	35–39	239	(64.3)	0.97	(0.88–1.07)		1.00	(0.91–1.09)	
	≥40	61	(45.9)	0.69	(0.57–0.84)	0.003	0.73	(0.59–0.89)	0.006
Ethnic group	European	800	(64.2)	Reference					
	Māori	42	(50.0)	0.78	(0.63–0.97)				
	Other	42	(53.2)	0.83	(0.67–1.02)	0.020			
Deprivation	Low (deciles 1–3)	392	(68.1)	Reference					
	Medium (deciles 4–7)	350	(59.9)	0.88	(0.81–0.96)				
	High (deciles 8–10)	138	(57.0)	0.84	(0.74–0.95)	0.002			

Other risk determinants									
Current smoker	No	739	(65.0)	Reference					
	Yes	145	(53.3)	0.82	(0.73–0.92)	0.001	0.86	(0.77–0.96)	0.009
BMI category, range (kg/m²)	Underweight, <18.5	17	(58.6)	0.89	(0.66–1.22)		0.89	(0.66–1.20)	
	Normal, 18.5–24.9	509	(65.5)	Reference					
	Overweight, 25.0–29.9	163	(66.5)	1.02	(0.91–1.13)		1.01	(0.92–1.11)	
	Obese class I, 30.0–34.9	109	(65.7)	1.00	(0.89–1.13)		1.00	(0.90–1.12)	
	Obese class II, 35.0–39.9	30	(50.0)	0.76	(0.59–0.99)		0.75	(0.58–0.97)	
	Obese class III, ≥40.0	14	(26.9)	0.41	(0.26–0.65)	0.001	0.42	(0.27–0.67)	0.002
Diagnostic variables									
Duration of infertility (years)	<2	366	(61.2)	Reference					
	2–4	307	(63.3)	1.03	(0.94–1.14)				
	>4	155	(66.2)	1.08	(0.97–1.21)	0.375			
Severe tubal/peritoneal disorder	No	754	(61.9)	Reference					
	Yes	130	(68.4)	1.11	(0.99–1.23)	0.063			
Severe endometriosis	No	857	(62.3)	Reference					
	Yes	27	(79.4)	1.27	(1.07–1.52)	0.007			
Severe ovulation disorder	No	829	(62.3)	Reference					
	Yes	55	(70.5)	1.13	(0.97–1.31)	0.104			

Table 4.13 continued		Number of patients receiving treatment (Prevalence, %)		Unadjusted*			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Severe semen disorder	No	661	(59.8)	Reference					
	Yes	223	(73.4)	1.23	(1.13–1.33)	<0.001			
Severe other infertility	No	865	(62.7)	Reference					
	Yes	19	(65.5)	1.05	(0.80–1.37)	0.746			
Severe unexplained infertility	No	755	(61.7)	Reference					
	Yes	129	(69.0)	1.12	(1.00–1.24)	0.041			
Number of severe diagnoses	0	453	(55.5)	Reference					
	1	409	(74.0)	1.33	(1.23–1.44)				
	≥2	22	(55.0)	0.99	(0.74–1.32)	<0.001			
Number of diagnoses	<2	609	(58.8)	Reference					
	≥2	275	(73.5)	1.25	(1.15–1.35)	<0.001			
Combined diagnostic score	Minimal	53	(30.3)	Reference					
	Mild	59	(49.2)	1.62	(1.22–2.17)		1.49	(1.11–1.99)	
	Moderate	198	(64.1)	2.12	(1.66–2.69)		2.05	(1.61–2.61)	
	Severe	486	(72.1)	2.38	(1.89–3.00)		2.28	(1.81–2.88)	
	Very severe	88	(67.2)	2.22	(1.72–2.86)	<0.001	2.27	(1.76–2.94)	<0.001

Treatment variables						
Qualified for public funding	No	154	(49.7)	Reference		
	Yes	730	(66.4)	1.34	(1.19–1.51)	<0.001

* *All independent variables with an unadjusted p<0.20 were tested for inclusion in the adjusted model, but only those that improved the model fit (as assessed by a reduced AIC) remained in the model and were reported in the final model.*

† *Simultaneously adjusted for all variables reported in the adjusted analysis.*

4.4.9 Predictors of resolved infertility

A live birth (resolved infertility) was the end point of care for 763 (54.2%) of the 1,409 OFS patients.

Table 4.14 on page 183 shows the unadjusted and adjusted relative risks of resolving infertility by selected demographic characteristics, other risk determinants, diagnoses, funding eligibility, predominant treatment and duration of care with the OFS.

Unadjusted regression analysis showed all demographic factors except parity were significantly associated with resolution of infertility. Not being in a relationship was associated with a reduced chance of resolution compared with those in a heterosexual relationship, as was being aged 35 years and over compared with age 30–34 years and being in the medium or high deprivation groups compared with the low deprivation group (Wald tests all $p<0.05$). Women of Māori ethnicity also had significantly decreased resolution compared with women of European ethnicity (Wald test $p=0.022$). Both having a BMI of 35 kg/m^2 or more (compared with the normal weight category) and being a smoker (compared with non-smoker) were significantly associated with a reduction in resolution (Wald tests $p=0.004$ and $p=0.014$ respectively).

Increasing duration of infertility was associated with a reduction in the likelihood of infertility resolution (Wald test $p<0.001$). Severe tubal/peritoneal disorder, endometriosis, semen disorder and unexplained infertility diagnoses were all associated with a reduced likelihood of infertility resolution (Wald tests all $p<0.01$). A decreasing level of infertility resolution was also associated with having one or more severe diagnoses (compared with none), and increasing combined diagnostic score (Wald tests both $p<0.001$). Qualifying for publicly funded ARTs and receiving any form of treatment were both associated with an increased resolution of infertility (Wald tests both $p<0.001$). Spending more than four years in care with the OFS was associated with a significant decrease in infertility resolution compare to spending six months or less in care (Wald test $p<0.001$).

A multivariate model was built to simultaneously adjust for all of these predictors, starting with the diagnostic and treatment predictors. To avoid colinearity issues, only diagnostic score and duration of infertility were fitted. Duration of infertility was not significant, possibly because the diagnostic score accounts for duration of infertility, as this is the measure for severity of unexplained infertility. Following this, predominant treatment, time in care, funding eligibility, BMI category, smoking, age group, relationship type, deprivation group, ethnicity and parity were added stepwise with the model AIC values determining which variables significantly improved the model's fit. Of these variables, funding eligibility, BMI category, smoking, ethnicity and parity did not contribute to a significant improvement in the model. It appeared that the unadjusted relationship with funding was probably due to this being on the casual pathway from age to treatment (with those aged 40 or more years not able to receive public funding). Eligibility for treatment would also likely explain the lack of association with smoking and BMI in the adjusted model.

The final model included relationship type, age group, deprivation, diagnostic score, predominant treatment and duration of care. This model showed that compared with being in a heterosexual relationship, same sex couples and women not in a relationship were only half as likely to resolve their infertility (RR 0.49, 95% CI 0.33–0.74). Increasing age was associated with decreasing resolution of infertility; being aged 35–39 years and 40 years and over compared with age 30–34 years had relative risks of 0.69 (95% CI 0.61–0.78) and 0.34 (95% CI 0.25–0.47) respectively. Increasing deprivation was associated with a more modest reduction in the likelihood of infertility resolution, with a 25% reduction in resolution for those of high deprivation compared with low deprivation (RR 0.75 95% CI 0.64–0.87). Increasing combined diagnostic score was associated with reducing level of resolution; the likelihood of pregnancy was almost halved for those with the relatively common score of 'severe' compared with those in the 'minimal' category (RR 0.57, 95% CI 0.49–0.66). Increasing level of treatment predominance was strongly associated with increasing resolution of infertility; comparing IVF to no treatment gave a relative risk of 2.05 (95% CI 1.77–2.37). Increasing duration of care was associated with both a decrease in the level of infertility resolution, and

increasing uptake of more complex treatments (such as IVF), and hence met the prerequisites to be a potential confounder of the relationship between treatment and resolution. Adjustment for duration of care in the multivariate model showed that the relationship between treatment and infertility resolution was under estimated in unadjusted analyses due to this confounding effect. In the final model duration of care was also strongly associated with resolution of infertility; there was a 67% reduction in the level of resolution for patients who spent four or more years with the OFS, compared with those patients who spent six months or less in care (RR 0.33, 95% CI 0.24–0.43).

Resolution of infertility was further analysed with Cox's proportional hazards and competing risk regression (refer to Appendices J and K for methods and the results table). For all patients, the overall rate of resolution was 33.2 (95% CI 30.9–35.6) live births per 100 person years of observation. Rephrased, this equates approximately to one in three women in care at the OFS experiencing a live birth over a year.

Unadjusted competing risk regression analysis provided very similar results to the Poisson modelling. Following stepwise construction of a multivariate model, the final model included relationship type, age group, deprivation, BMI and diagnostic score. This model was rerun as a Cox's proportional hazards regression and comparison of the estimates revealed very little difference between these two models; there was no evidence of an effect due to a competing risk of a couple separating (data not shown). Interpretation of the competing risk multivariate model was also very similar to that for Poisson regression, apart from the significance of parity and the exclusion of treatment data for technical reasons (timing and duration of exposure to the predominant treatment was not available).

The cumulative incidence function curves for the adjusted variables in the final competing risk model are presented in Figure 4.2 on page 187. The curves demonstrate the strong associations between infertility resolution and these variables, with the exception of deprivation, which had a more modest effect.

Table 4.14: Unadjusted and adjusted relative risk of resolution of infertility by demographic factors, other risk determinants, duration of infertility, diagnoses, funding eligibility and treatment type

		Number of patients who had a live birth (Cumulative incidence, %)		Unadjusted*			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Demographic factors									
Parity	0	533	(55.8)	Reference					
	≥1	230	(50.7)	0.91	(0.82–1.01)	0.076			
Relationship type	Heterosexual	750	(55.1)	Reference					
	Same-sex/No relationship	13	(27.1)	0.49	(0.31–0.78)	0.003	0.49	(0.33–0.74)	<0.001
Age group (years)	<30	263	(64.3)	1.03	(0.93–1.13)		1.07	(0.98–1.17)	
	30–34	310	(62.6)	Reference					
	35–39	161	(43.3)	0.69	(0.60–0.79)		0.69	(0.61–0.78)	
	≥40	29	(21.8)	0.35	(0.25–0.48)	<0.001	0.34	(0.24–0.43)	<0.001
Ethnic group	European	693	(55.6)	Reference					
	Māori	35	(41.7)	0.75	(0.58–0.97)				
	Other	35	(44.3)	0.80	(0.62–1.03)	0.022			
Deprivation	Low (deciles 1–3)	352	(61.1)	Reference					
	Medium (deciles 4–7)	310	(53.1)	0.87	(0.79–0.96)		0.93	(0.85–1.02)	
	High (deciles 8–10)	98	(40.5)	0.66	(0.56–0.78)	<0.001	0.75	(0.64–0.87)	<0.001

Table 4.14 continued		Number of patients who had a live birth (Cumulative incidence, %)		Unadjusted*			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Other risk determinants									
Current smoker	No	635	(55.9)	Reference					
	Yes	128	(47.1)	0.84	(0.74–0.97)	0.014			
BMI category, range (kg/m²)	Underweight, <18.5	11	(37.9)	0.67	(0.42–1.06)				
	Normal, 18.5–24.9	443	(57.0)	Reference					
	Overweight, 25.0–29.9	140	(57.1)	1.00	(0.88–1.14)				
	Obese class I, 30.0–34.9	96	(57.8)	1.01	(0.88–1.17)				
	Obese class II, 35.0–39.9	25	(41.7)	0.73	(0.54–0.99)				
	Obese class III, ≥40.0	14	(26.9)	0.47	(0.30–0.74)	0.004			
Diagnostic variables									
Duration of infertility (years)	<2	363	(60.7)	Reference					
	2–4	267	(55.1)	0.91	(0.82–1.01)				
	>4	94	(40.2)	0.66	(0.56–0.78)	<0.001			
Severe tubal/ peritoneal disorder	No	683	(56.0)	Reference					
	Yes	80	(42.1)	0.75	(0.63–0.89)	0.001			
Severe endometriosis	No	755	(54.9)	Reference					
	Yes	8	(23.5)	0.43	(0.23–0.79)	0.006			

Severe ovulation disorder	No	726	(54.6)	Reference					
	Yes	37	(47.4)	0.87	(0.68–1.10)	0.252			
Severe semen disorder	No	620	(56.1)	Reference					
	Yes	143	(47.0)	0.84	(0.74–0.95)	0.008			
Severe other infertility	No	747	(54.1)	Reference					
	Yes	16	(55.2)	1.02	(0.73–1.42)	0.910			
Severe unexplained infertility	No	687	(56.2)	Reference					
	Yes	76	(40.6)	0.72	(0.60–0.87)	<0.001			
Number of severe diagnoses	0	487	(59.7)	Reference					
	1	268	(48.5)	0.81	(0.73–0.90)				
	≥2	8	(20.0)	0.34	(0.18–0.62)	<0.001			
Number of diagnoses	<2	557	(53.8)	Reference					
	≥2	206	(55.1)	1.02	(0.92–1.14)	0.672			
Combined diagnostic score	Minimal	109	(62.3)	Reference					
	Mild	70	(58.3)	0.94	(0.77–1.13)		0.76	(0.64–0.91)	
	Moderate	196	(63.4)	1.02	(0.88–1.18)		0.73	(0.63–0.85)	
	Severe	346	(51.3)	0.82	(0.72–0.94)		0.57	(0.49–0.66)	
	Very severe	42	(32.1)	0.51	(0.39–0.68)	<0.001	0.43	(0.33–0.55)	<0.001

Table 4.14 continued		Number of patients who had a live birth (Cumulative incidence, %)		Unadjusted*			Adjusted†		
				RR	(95 CI%)	P-value	RR	(95 CI%)	P-value
Treatment variables									
Qualified for public funding	No	113	(36.7)	Reference					
	Yes	650	(58.9)	1.62	(1.39–1.89)	<0.001			
Predominant treatment	None	207	(43.0)	Reference					
	IVF	277	(56.9)	1.32	(1.16–1.50)		2.05	(1.77–2.37)	
	Surgery	71	(59.7)	1.39	(1.16–1.66)		1.88	(1.55–2.28)	
	IUI/DI	90	(67.7)	1.57	(1.35–1.84)		1.83	(1.58–2.13)	
	OI	102	(70.8)	1.65	(1.42–1.91)		1.61	(1.39–1.86)	
	Other	16	(35.6)	0.83	(0.55–1.24)	<0.001	0.90	(0.63–1.29)	<0.001
Duration of care with the OFS (months)	<6	211	(52.9)	Reference					
	6–12	157	(62.3)	1.18	(1.03–1.35)		0.97	(0.86–1.09)	
	13–24	204	(60.9)	1.15	(1.01–1.31)		0.89	(0.78–1.00)	
	25–48	153	(53.7)	1.02	(0.88–1.17)		0.70	(0.60–0.81)	
	>48	38	(27.5)	0.52	(0.39–0.69)	<0.001	0.33	(0.24–0.43)	<0.001

* *All independent variables with an unadjusted p<0.20 were tested for inclusion in the adjusted model, but only those that improved the model fit (as assessed by a reduced AIC) remained in the model and were reported in the final model.*

† *Simultaneously adjusted for all variables reported in the adjusted analysis .*

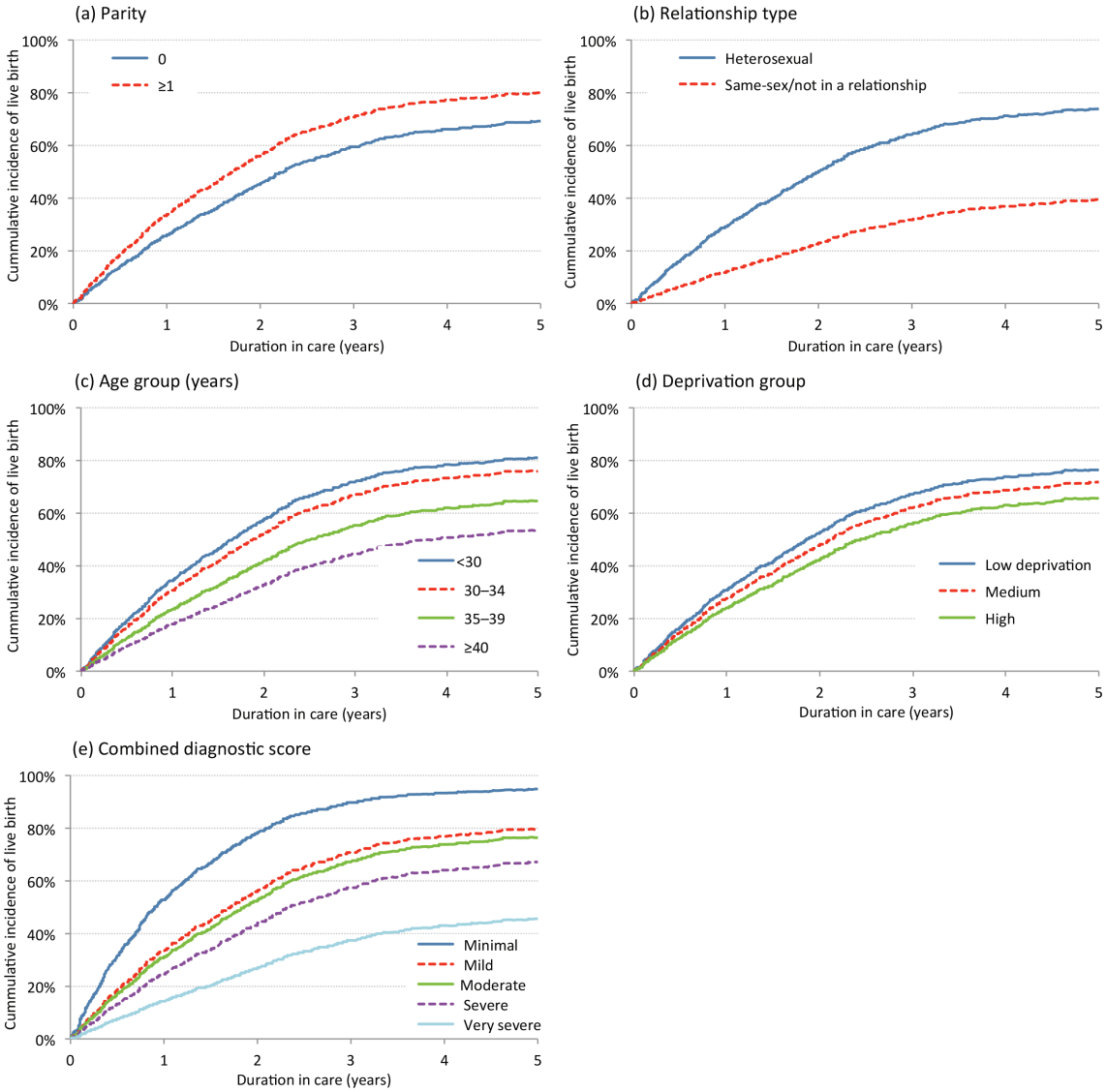


Figure 4.2: Cumulative incidence function curves for predictors of infertility resolution: (a) parity; (b) relationship type; (c) age group; (d) deprivation group; and (e) combined diagnostic score

4.5 Discussion

4.5.1 Main Findings

Due to the volume of analyses presented in Chapter Four, the main finding are summarised in Table 4.15.

Table 4.15: Summary of main finding on outcomes for patients of the OFS

Outcome	Prevalence n (%)	Significant predictors of the outcome		
		Predictor		Adjusted RR (95% CI)
Programme withdrawal	229 (16.3)	Ethnic group	European	Reference
			Māori	1.55 (1.03–2.32)
			Other	1.49 (0.92–1.92)
		Deprivation	Low	Reference
			Medium	1.16 (0.87–1.57)
			High	1.67 (1.18–2.34)
		BMI range (kg/m^2)	<18.5	1.42 (0.71–2.81)
			18.5–24.9	Reference
			25.0–29.9	0.88 (0.61–1.28)
			30.0–34.9	1.14 (0.78–1.67)
			35.0–39.9	1.83 (1.17–2.87)
			≥40.0	2.04 (1.32–3.18)
		Current smoker	No	Reference
			Yes	1.44 (1.09–1.92)
Receiving treatment	844 (59.9)	Parity	0	Reference
			≥1	0.83 (0.75–0.91)
		Age group (years)	<30	0.92 (0.84–1.01)
			30–34	Reference
			35–39	1.00 (0.91–1.09)
			≥40	0.73 (0.59–0.89)
		BMI range (kg/m^2)	<18.5	0.89 (0.66–1.20)
			18.5–24.9	Reference
			25.0–29.9	1.01 (0.92–1.11)
			30.0–34.9	1.00 (0.90–1.12)
			35.0–39.9	0.75 (0.58–0.97)
			≥40.0	0.42 (0.27–0.67)

Table 4.15 ***continued***

Outcome	Prevalence n (%)	Significant predictors of the outcome		
		Predictor		**Adjusted RR (95% CI)**
		Current smoker	No	Reference
			Yes	0.86 (0.77–0.96)
		Combined diagnostic score	Minimal	Reference
			Mild	1.49 (1.11–1.99)
			Moderate	2.05 (1.61–2.61)
			Severe	2.28 (1.81–2.88)
			Very severe	2.27 (1.76–2.94)
Resolving infertility with a live birth	763 (54.2)	Relationship type	Heterosexual	Reference
			Same-sex/No relationship	0.49 (0.33–0.74)
		Age group (years)	<30	1.07 (0.98–1.17)
			30–34	Reference
			35–39	0.69 (0.61–0.78)
			≥40	0.34 (0.24–0.43)
		Deprivation	Low	Reference
			Medium	0.93 (0.85–1.02)
			High	0.75 (0.64–0.87)
		Combined diagnostic score	Minimal	Reference
			Mild	0.76 (0.64–0.91)
			Moderate	0.73 (0.63–0.85)
			Severe	0.57 (0.49–0.66)
			Very severe	0.43 (0.33–0.55)
		Predominant treatment	None	Reference
			IVF	2.05 (1.77–2.37)
			Surgery	1.88 (1.55–2.28)
			IUI/DI	1.83 (1.58–2.13)
			OI	1.61 (1.39–1.86)
			Other	0.90 (0.63–1.29)
		Duration of care with the OFS (months)	<6	Reference
			6–12	0.97 (0.86–1.09)
			13–24	0.89 (0.78–1.00)
			25–48	0.70 (0.60–0.81)
			>48	0.33 (0.24–0.43)

The median duration of infertility at presentation at the OFS for first referral was relatively stable from 1998–2005, with the median duration of infertility being two years. These findings differ from trends observed in other countries that suggest women have been presenting with ever shorter durations of infertility over time. However, this may be a reflection of the conservative approach to referral in Otago and Southland (Gillett, 2014b) and the relatively short duration of the study. Overall, two-thirds of referrals were for primary infertility and one-third for secondary infertility, although some of the women classified as having primary infertility may have had previous pregnancies that did not end in a live birth, these were not recorded by the OFS. Just over a third of women presenting for their first appointment were aged 35 years or more, over 20% were obese, and just under 20% were smokers, all of which are recognised as factors that can compromise fertility. The prevalence of these factors amongst infertile women may be underestimated if referral is influenced by age, BMI or smoking status.

The most common diagnoses amongst women/couples attending the OFS were semen disorder at 36.5% (this includes women without a heterosexual partner), followed by ovulation disorder (25.1%) and tubal/peritoneal disorder (20.3%). The proportions of infertile women with tubal/peritoneal disorder and semen disorder were higher than those seen in clinical settings in other developed nations (Weiss *et al.*, 1992, Wilkes *et al.*, 2009). However, it is not known if, in those studies, sterilisation was also considered as a tubal/semen disorder. Women without a male partner were included in the denominator for the calculation of the prevalence of diagnoses; therefore, the prevalence of the various diagnoses would be slightly higher if the sample of patients was restricted to women in a heterosexual relationship only. Infertility was unexplained in 14.9% of patients and a further 2.8% had no diagnoses, but did not have a complete investigation.

Multiple diagnoses were common, with a quarter of patients having more than one diagnosis. Half of the patients had at least one severe diagnosis. Two other clinical studies have reported on the prevalence on multiple diagnoses with results that differed markedly from each other; a study in England reported a prevalence of 7.0%, whereas an earlier study in the USA reported a prevalence of 40.0%

(Verkauf, 1983, Wilkes *et al.*, 2009). CPAC assessment summarises all diagnoses and their severities to provide an overall combined diagnostic score, for OFS patients 57.1% had a severe to very severe overall diagnostic classification.

Over three-quarters of women were eligible for public funding of ARTs, although for many this was more than a year after their initial referral appointment, and for those with BMIs outside the optimum range or who smoked, this was dependent on meeting the BMI and non smoking requirements. Over a third of patients had no treatment or were provided other help such as weight management advice. Of the 62.7% of women treated, half had or eventually had (if other treatment failed) IVF.

The two models determining which factors were associated with withdrawal from services and which factors were associated with having treatment showed that a BMI of 35kg/m^2 or more and being a smoker were both significantly associated with not receiving any treatment or being offered other forms of help. These factors were in turn associated with higher levels of withdrawal from the OFS before completion of care. Women who smoked or had a BMI outside of the accepted range could not access publicly funded treatment, which may have influenced their decision to voluntarily withdraw. Equally the reduced likelihood of treatment success for these women may have influenced their decision. It is important to note, however, that women who smoked and/or had an unacceptable BMI were not removed from the programme (unless they themselves had withdrawn); they were put on active review until such time as these factors were sufficiently improved.

High deprivation was also associated with increased risk of withdrawal and decreased likelihood of treatment. High deprivation is known to be associated with an increased risk of smoking and higher BMIs, but this effect was controlled for in the adjusted estimates and, therefore, does not explain these associations. The costs of seeking care (both publicly and privately funded) and reduced opportunity to seek care (such as having the appropriate transportation and leave from employment) may have negatively impacted on the ability of more highly deprived women/couples to attend the clinic and have treatment.

Having previous children, being aged 40 or more years and low overall diagnostic severity were all associated with reduced treatment uptake (but not with increased withdrawal). Chandra and Stephen similarly found in their population-based study in the USA that having treatment was predicted by age and parity (Chandra and Stephen, 2010).

Overall, a live birth was achieved by 54.2% of patients while in care with the OFS, over half of these live births resulted from treatment. Approximately one in three women in care at the OFS experienced a live birth over a year. This level of infertility resolution is consistent with population-based studies which reported rates of conception after infertility were above 50% (refer to Section 2.7.1 on page 50). The likelihood of infertility resolution was influenced by a number of factors, but the most strongly reduced likelihoods of resolution were in patients who were not in a heterosexual relationship, who were aged 35 years and over, who had a severe/very severe combined diagnostic score, or who did not receive some form of treatment. As those women not in a heterosexual relationship could not resolve their infertility without treatment, this result was expected, as were age and severe infertility, both being known risk determinants for reduced fecundity (refer to Figure 4.1). Whilst not very common, diagnosed severe endometriosis was also associated with a very strong risk of unresolved infertility in the unadjusted estimates.

High deprivation was associated with a more moderately reduced likelihood of a live birth; this was after taking into account the effect of treatment, with treatment being less likely for highly deprived patients. The mechanism by which deprivation impacts of the likelihood of a resolving infertility needs further investigation, although some of this association may be explained by a residual confounding effect of smoking and BMI which were not included in the final model for infertility resolution.

4.5.2 Study strengths and limitations

The present study had several strengths and limitations that warrant further consideration.

Strengths

The study monitored a relatively large number of patients, with all patients followed until conclusion of their treatment programme or for at least five years and, as such, provides an excellent opportunity to model predictors of withdrawal, receiving treatment and resolving infertility. This is one of the only clinical studies that have allowed a comprehensive epidemiological analysis of infertility care and outcomes; only a few studies were identified that could be compared to the various outcomes examined, and often these studies were much smaller, with poorly defined measures and some of which were relatively old.

Diagnoses were not self-reported as occurs in the majority of population-based studies, but provided by objective clinical assessment by just two clinicians, which should minimise variations. Assessment of the impact of multiple diagnoses and their severities was simplified by the availability of a previously validated measure: The combined diagnostic severity score.

NHI-derived ethnicity data were used, providing a more robust ethnicity measure than a one-time measure that would be provided by clinical data. The study was also able to use NHI data to link to a well-characterised area-based measure of SES, the deprivation index, thereby providing unique insights into infertility care by SES in New Zealand.

Representativeness of patients

As the underlying prevalence of infertility in the population is unknown, there was little evidence to assess whether clinic access was equitable by such characteristics as ethnicity and deprivation across the Otago and Southland regions. Just 5.9% of women attending the clinic were Māori compared with 8.6% of the resident female population aged 15–49 years in the Otago and Southland regions in 2006. The deprivation profile of patients was skewed towards those from least deprived areas, 29.0% were from the two least deprived deciles, and only 6.6% from the two most deprived deciles. The region's 2006 census data show that 22.3% of the population were in the two least deprived deciles and 15.7% of the population were in the two most deprived deciles. This explains some, but not all of the

difference in clinic access. Evidence from England suggested occupational social class was related to service seeking from GPs, with higher classes more likely to access services. However, these differences did not persist in referral to hospital services (Gunnell and Ewings, 1994). A study in the USA showed higher service seeking was related to higher income (Chandra and Stephen, 2010).

In the present study, it is not possible to discern if these differences in demographics between the regional population and women attending the clinic were due to there being different underlying levels of infertility by deprivation and ethnicity, or other explanations, such as a lack of equitable access as seen in England and the USA.

Definition of primary and secondary infertility

Using previous live birth instead of pregnancy to define primary infertility will have led to some women being classified as having primary infertility who actually had secondary infertility according to the accepted definitions of primary and secondary infertility. Therefore, the difference in the number of primary and secondary cases was exaggerated.

Accuracy of self-reported data and subjective measures

Duration of infertility and being a current smoker were self-reported by the patient, and required honesty, but according to the assessing clinician obvious deceptions were not evident (Gillett *et al.*, 2012). Furthermore, comparison of the prevalence of current smoking amongst patients and data from the New Zealand Health Survey for Otago and Southland in 2006–7 showed similar results of 19.2% and 20.7% respectively (Ministry of Health, 2008). The measures of smoking and BMI were both recorded at the patient's first visit only, but these are not fixed exposures. Any variation in smoking and BMI over time and their effects on receiving treatment and resolving infertility could not be assessed.

The combined diagnostic score did require some subjective assessment of clinical information, and was a theoretical model only. One particular issue of note was that all patients received a score of at least minimal severity for unexplained

infertility (due to requirements of the CPAC tool and the definition used for unexplained infertility). This unexplained infertility score was combined with all other diagnoses to calculate the diagnostic score, despite the fact that unexplained infertility by definition is a mutually exclusive diagnosis. However, this CPAC tool and diagnostic score were previously assessed and correlated well to the chance of spontaneous pregnancy, which suggests the score was robust (although the CPAC tool was further refined with a slight alteration of the semen and ovulation criteria after the conclusion of data collection for this study in 2005) (Gillett *et al.*, 2012).

Other limitations

Despite the large sample size, the present study lacked power to investigate differences by ethnic group due to the small proportions who were not in the European category. Furthermore (in relation to the competing risk model for infertility resolution), loss to follow up could be related to the likelihood of resolution of infertility, which would introduce bias. It would have been useful to have more details about reason for withdrawal to assess this. However, in the context of a cohort study the loss to follow up was minimal (16.4%), therefore any bias introduced should only have had a minimal impact on the model estimates. The study was also limited to the data that had been collected for evaluating the performance of the infertility CPAC, therefore other areas of interest such as distress/anxiety, more detailed information about patient withdrawal, the effect of non-treatment interventions and the impact of failed treatment could not be explored. Furthermore, data providing an indication of the distance of the patient's residential address from the clinic were not available; therefore, the impact of this on withdrawal and treatment uptake could not be evaluated.

4.5.3 Summary

This study of a large cohort (N=1,407) of women/couples seeking specialist care for infertility revealed that the pathways to withdrawal for infertility care, receiving treatment and resolution of infertility are intertwined and complicated, but can all be partially explained by a number of factors, most commonly deprivation and BMI.

Sixteen point two per cent (229) of patients withdrew from the programme, the risk of doing so was elevated amongst women in the highest deprivation group (RR 1.67, 95% CI 1.18–2.34, when compared with the lowest deprivation group) and amongst women of Māori compared with European ethnicity (RR 1.55, 95% CI 1.03–2.32). The risk of withdrawal was also increased amongst women who were least likely to be able to access public funding for treatment: Those who smoked compared with non-smokers (RR 1.44, 95% CI 1.09–1.92); and those who were obese, with women who had a BMI of 40kg/m^2 or more twice as likely as those with a normal BMI to voluntarily withdraw (RR 2.04, 95% CI 1.32–3.18).

Almost two-thirds (62.7%, 884) of women received some form of treatment, with the likelihood of being treated increased amongst those who had a more than minimal diagnostic severity and decreased amongst women who were obese. Age was also shown to impact on treatment uptake in this study, with those who were particularly young or particularly old less likely to receive treatment.

Overall, 763 (54.2%) patients resolved their infertility at a rate of 33.2 (95% CI 30.9–35.6) live births per 100 person years of observation. Increasing age, deprivation and diagnostic severity all independently contributed to a decreased likelihood of infertility resolution in this study, whereas receiving treatment increased the likelihood of infertility resolution.

The study had a number of strengths compared with other clinical studies of infertility. Diagnoses and their impact on treatment uptake and resolution of infertility can be difficult to assess, as frequently patients have more than one diagnosis that contributes to their infertility. This study was in a unique position to be able to use a previously validated combined diagnostic score, which accounts for the effect of multiple diagnoses and their severity, allowing a robust assessment of the impact of diagnostic severity. This study was also able to link to NHI data to provide more robust ethnicity data and a surrogate marker of SES.

The information provided by the study's models of programme withdrawal, treatment uptake and resolution of infertility is unique, and, in particular, will be valuable for patients and clinicians when assessing a patient's likelihood of being

able to have a child in the future. However, further research is needed at a national level in New Zealand, or in other regions outside of Otago and Southland, to validate these results and provide more information about the impact of ethnicity on withdrawal, treatment uptake and infertility resolution and to determine the mechanisms by which SES is impacting on resolution of infertility.

CHAPTER FIVE:

COMPARISON OF THE POPULATION AND CLINIC-BASED STUDIES

Chapter Five provides a brief analysis comparing related findings from the population and clinic-based infertility studies, and discusses the similarities and differences in the findings of the two studies.

5.1 Introduction

A common criticism of cross-sectional surveys is the possibility of inaccurate recall of past events, especially with respect to self-reported diagnoses/health measures (Bergmann *et al.*, 1998, Baker *et al.*, 2004), and these inaccuracies may introduce systematic bias (Webb *et al.*, 2005a). In addition, cross-sectional studies can be subject to selection bias, especially studies with a very low response rate. A response rate of less than 70% is considered sub-optimal (Rubenfeld, 2004), as the sample is considered to be less likely to be representative of the population, hence significant uncertainty about the validity of the study findings can be introduced (Webb *et al.*, 2005c). Although, more recently some evidence has suggested that surveys with response rates below 70% can provide acceptable results (Sierles, 2003, Choung *et al.*, 2013).

Comparing some aspects of the infertility data from participants in the population-based survey in Otago and Southland with the OFS clinic patient data, which covers the same region, allows for an assessment of potential biases in self-reports. Women selected to participate in the cross-sectional survey were aged 25–50 years in the 2010 electoral roll, meaning they would have been born between 1960–1985. Years of birth for women attending the OFS ranged from 1948–1987. Restricting to OFS patients who were born in a similar period allows for a reasonable comparison with the survey data; these women would have been eligible to be in the population-based survey, assuming they were still residing in Otago or Southland at the end of 2010. Therefore, the aim of this brief analysis is to describe the similarities and differences between comparable measures from the population and clinic-based studies.

5.2 Methods

For the purpose of comparing the reports of infertility-related measures in the two studies, data for the OFS clinic study were limited to that for patients born between 1960 and 1985. Data from the cross-sectional survey were limited to participants who had ever attended an infertility specialist for difficulties conceiving. Data were then adjusted from the cross-sectional survey to conform to the data available from the OFS, where possible, as described. Differences between survey and clinic data were tested for statistical significance using Pearson's χ^2 tests. All analyses were performed in STATA 12.1/IC.

5.2.1 Infertility diagnoses

First referral to the OFS captured data over what could have been a long period (although diagnosis was usually completed within two years of first referral). Some women may have defined trying to conceive over a long period as more than one attempt if describing their experiences. Therefore, for the survey diagnosis data, any self-reported diagnoses on women's first and subsequent (if applicable) specialist visits were included for comparison. These previously constructed variables are described in Section 3.3.12 on pages 83–84.

The OFS diagnosis variables are described in Section 4.3.4 on pages 150–151. For the purpose of this comparison the categories on reversal of sterilisation were omitted as these data were not available from the survey, and the categories of 'unexplained infertility' and 'incomplete investigation' and 'no diagnosis' were combined to compare with the survey's 'unknown' category.

5.2.2 Uptake of treatment

Women were able to self-report multiple treatments across multiple episodes of infertility in the cross-sectional survey. As outlined in Section 5.2.1, data were included for both the first and any subsequent reported specialist visits. A new variable was constructed to prioritise treatments into the predominant treatment types as follows: Predominant treatment was coded as IVF if women ever reported

receiving IVF; if IVF was not reported then predominant treatment was coded as surgery if surgery was ever reported; the predominance order of the remaining categories was IUI/DI; then drugs/OI; and last was other treatment. Any remaining women were considered not to have received treatment. The equivalent variable was already available for the clinic data, as described in Section 4.3.5 on page 152.

5.2.3 Resolution of infertility

A variable was generated from the survey data to determine if a live birth had been reported since a women's first reported attendance with a specialist for infertility. This variable was already available for clinic patient data as described in Section 4.3.6 on pages 153–154.

5.3 Results

Of the 1,409 OFS patients, 1,321 were born between 1960 and 1985. Amongst survey participants who reported difficulties conceiving, 117 had seen a specialist provider for these difficulties.

5.3.1 Infertility diagnoses

Table 5.1 (overleaf) shows the self-reported infertility diagnoses by survey participants and the diagnoses recorded for clinic patients.

The most common diagnoses in both the survey participants and clinic patients were male factor (33.3 and 36.9% respectively) and ovulation disorders (24.6 and 25.4% respectively). All female factor, male factor and combined factor diagnoses were slightly more common in clinic patients than survey participants, however, none of these difference were statistically significant. Other causes were reported more commonly amongst survey participants (16.7%) than amongst clinic patients (5.0%); this difference was highly significant (Pearson's χ^2 $p<0.001$). Unknown cause was also more common amongst survey participants, but this was not statistically significant.

Multiple diagnoses were reported by 28 (24.6%) of the survey participants and recorded for 347 (27.0%) of the clinic patients; this small difference being non-significant (Pearson's χ^2 p=0.576).

Table 5.1: Diagnoses reported by survey participants/recorded for clinic patients

Causes of infertility	Survey participants n (%)	Clinic patients n (%)	P-value
Female factor			
Ovulation disorder	28 (24.6)	335 (25.4)	0.592
Endometriosis	21 (18.4)	266 (20.1)	0.660
Tubal/peritoneal	16 (14.0)	277 (21.0)*	0.078
Any female factor	66 (57.9)	741 (56.1)	0.710
Male factor	38 (33.3)	486 (36.8)*	0.462
Combined factor	13 (11.4)	192 (14.5)	0.359
Other			
Other cause	19 (16.7)	66 (5.0)	<0.001
Unknown	27 (23.7)	225 (17.0)†	0.073
Total	114‡	1,321	

* *Does not include reversal of sterilisation.*

† *Unknown includes unexplained infertility and those without a diagnosis who had not had completed investigations.*

‡ *Three women who attended a specialist did not answer the question on diagnoses.*

5.3.2 Uptake of treatment

Table 5.2 shows the predominant infertility treatment self-reported by survey participants and that which was recorded for clinic patients.

IVF was similarly reported as being received by almost a third of survey participants and just over a third of clinic patients (Pearson's χ^2 p=0.457). There was also no difference in receiving IUI/DI between the studies, with 9.2% of participants and patients receiving this.

Surgery, however, was more common amongst survey participants (15.6%) than clinic patients (8.5%) (Pearson's χ^2 p=0.013); this was also true of receiving drugs

(21.1% versus 10.2%, Pearson's χ^2 p<0.001). The reverse was true for not receiving any treatment, 18.4% of survey participants reported this compared with 33.2% of clinic patients (Pearson's χ^2 p=0.001).

Table 5.2: The predominant treatment reported by survey participants/recorded for clinic patients

Predominant treatment	Survey participants n (%)		Clinic patients n (%)		P-value
IVF	35	(32.1)	471	(35.7)	0.457
Surgery	17	(15.6)	112	(8.5)	0.013
IUI/DI	10	(9.2)	121	(9.2)	1.000
Drugs or OI	23	(21.1)	135	(10.2)	<0.001
Other	4	(3.7)	44	(3.3)	0.850
No treatment	20	(18.4)	438	(33.2)	0.001
Total	109		1,321		

5.3.3 Resolution of infertility

Of the 117 survey participants who consulted a specialist for infertility, 64 (54.7%) reported a live birth following this episode of infertility. Of the 1,321 OFS patients, 743 (56.3%) resolved their infertility; this was not significantly different from the levels of resolution seen amongst the survey participants (Pearson's χ^2 p=0.747).

5.4 Discussion

5.4.1 Comparison of the two studies

Measures from the two studies compared very well and do not suggest any strong selection or information biases in the cross-sectional survey. This result occurred despite this survey having a response rate of around 60% and requiring participants to provide very detailed recall of their fertility histories.

The prevalence of the main diagnoses (ovulation disorder, endometriosis, tubal/peritoneal and male factor) were slightly lower in the survey participants

than amongst patients, but not significantly so. Some survey participants self-reported endometriosis, but not as an infertility diagnosis received from the specialist (they reported it in a general question about conditions that might affect fertility). It is possible that by asking about diagnoses as discrete events within each infertility episode, diagnoses that may have been made outside the specialist setting and/or that were not salient enough to attach to a particular event could be under-reported. This appears to be the case for endometriosis, but other conditions were not measured elsewhere. There was some evidence of recall and/or questionnaire interpretation issues, with many more women stating that they had an 'Other diagnosis' amongst survey participants than clinic attendees, suggesting that they could not recall their exact diagnosis and/or they were not aware of which category this would fall. Whilst not significantly different, also more women in the survey said the cause of their infertility was not known. It is possible that participants attending secondary care and/or gynaecologists rather than the infertility clinic for tertiary specialist care explains some of this increase in the other and unknown diagnosis categories, as it is likely that investigation would be more rigorous in a tertiary infertility care setting.

Amongst treatment data there was no difference in the frequency of having IVF between the two studies. However surgery was much greater amongst survey participants. It is possible that this is because participants in the survey reported diagnostic procedures that did not have a treatment element (e.g. investigation for laparoscopy) as surgery; this would also explain why fewer reported not having any treatment. Evidence for this is based on how many women reported laparoscopy as a surgical procedure in the general questions section. Also, a number of participants did not answer questions on treatment; as this was a check box question. These participants may have assumed that by not selecting any treatment they were reporting not having a treatment, or alternatively they could not remember and, therefore, did not answer. A significantly higher proportion of survey participants received drugs; this could have occurred as drugs (including those for ovulation induction) can be prescribed by secondary care providers (but other treatments are not available in the secondary care setting). It is plausible that some women included GP prescriptions. The inclusion of non-treatment

surgical procedures and prescriptions from secondary care providers and/or GPs could also explain why overall significantly fewer study participants reported having no treatment compared with clinic patients.

5.4.2 Strengths and limitations

The main strength of this analysis was in illustrating the validity of self-reported infertility experiences. Whilst minor differences were present, overall the main findings from the cross-sectional survey, such as the most common diagnoses, the proportion receiving ARTs and the proportion resolving infertility were very similar. This suggests it is reasonable to summarise the results from the two studies to give a comprehensive overview of infertility in the Otago and Southland regions when discussing the findings of these studies (refer to Chapter Seven).

There was some evidence of minor recall issues based on responses to questions on diagnoses and treatments, but overall the two studies provided very similar results, especially for more salient measures such as receiving IVF treatment. Issues comparing treatment data and deciphering what study participants may have included in each category illustrates the issues present when reviewing the infertility literature (refer to Section 2.7.1 on pages 49–50), in particular, defining what constitutes having received treatment.

5.4.3 Summary

The population and clinic-based studies provided a consistent representation of infertility causes and treatments in Otago and Southland.

CHAPTER SIX:

STUDY THREE: REVIEW OF HOSPITAL DISCHARGE DATA

Chapter Six outlines Study Three: A feasibility study on the utility of hospital discharge data on publicly funded admissions for infertility, pelvic inflammatory disease and ectopic pregnancy, for monitoring infertility and indicators of tubal factor infertility nationally. This chapter includes an introduction and literature review, and the objectives, methods and results of this study.

6.1 Introduction

For many diseases, trends in their occurrence, and other aspects of the descriptive epidemiology, can be obtained using hospital discharge data. This is because reliable information is obtained on the cause of admission at discharge, discharge diagnoses have been consistently recorded using internationally standardised classifications for many years and these data are readily available. Unfortunately similar information is generally not available for outpatient hospital attendances or GP visits.

National hospital discharge data, therefore, could potentially provide useful information on infertility, and other indicators of the risk of tubal factor infertility, in the absence of any national data from epidemiological studies. However, the current evidence suggests the surveillance and assessment of the burden of infertility in populations using routinely collected data such as hospital admissions is challenging; there were only a few published articles that analysed such data. The value of infertility data for monitoring outcomes (e.g. from *C. trachomatis* screening programmes) is not as good as that for ectopic pregnancy or PID, which probably accounts for the paucity in published data. Trends in publicly funded infertility hospitalisations in tertiary care are much more likely to be strongly influenced by health systems, funding policies, and changing technologies, particularly regarding diagnoses and treatments that can be offered that avoid inpatient care, particularly compared with ectopic pregnancy. Therefore, any

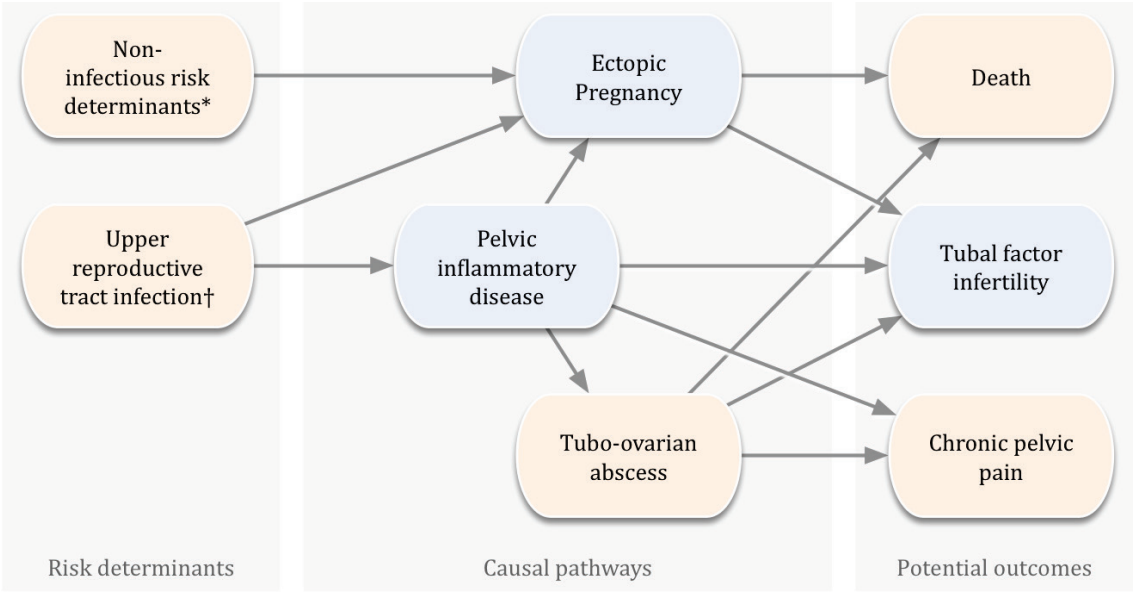
changes in infertility diagnoses trends could be due to a combination of these factors and/or a true change in the underlying prevalence of infertility. Furthermore, PID and ectopic pregnancy can be directly caused by *C. trachomatis*, whereas infertility is not directly caused by *C. trachomatis*, therefore, any change in the incidence of *C. trachomatis* would likely impact on the rates of PID and ectopic pregnancy more so than infertility.

6.1.1 Infertility hospitalisation data

The largest study that did report on infertility discharges, a cross-national study of six countries (Australia, Denmark, the Netherlands, New Zealand, Sweden and Switzerland) between 1999 and 2008, found that the rates of hospital admissions for infertility varied widely between countries and trends over time differed (Bender *et al.*, 2011). Supplementary data available for this study indicate that there was a significant decline in infertility hospitalisations from 1998–2008 in Australia, Denmark, New Zealand and Sweden. The Netherlands and Switzerland appeared to show a small increase over time. Morgan *et al*. (2011) further reports that in the Waikato, Bay of Plenty and Auckland regions of New Zealand, whilst the overall publicly funded infertility admissions fell, the rate was stable in women aged over 35 years. It is likely that this decline in New Zealand reflects a change in the balance of publicly funded versus privately funded infertility treatment (due to the introduction of CPAC for determining funding eligibility, see Section 4.1, pages 145–146) and a shift towards outpatient care and increasing IVF rather than declining infertility levels (Gillett, 2014a). Other data from New South Wales, Australia, suggest a stabilisation in the rapid decline of infertility hospitalisations seen in the late 1990s when inpatient care moved to outpatient treatment with ART, with no further declines seen between 2001 and 2008 (Liu *et al.*, 2012). This evidence suggests that infertility hospitalisation data are not likely to be very useful.

6.1.2 Pelvic inflammatory disease and ectopic pregnancy as risk indicators of tubal factor infertility risk

Unlike infertility hospital discharges, PID and ectopic pregnancy discharges have been more commonly examined in the published literature. These conditions share common causal pathways with tubal factor infertility as illustrated in Figure 6.1 (Gerbase *et al.*, 2006). Therefore, the hospital admissions data for PID and ectopic pregnancy may also provide an indication of the risk of tubal factor infertility.



Adapted from Gerbase et al. (2006).

* *Smoking, prior ectopic pregnancy, tubal surgery.*

† *Infection with C. trachomatis, N. gonorrhoea, normal vaginal flora.*

Figure 6.1: Pelvic inflammatory disease and ectopic pregnancy causal pathways

Pelvic inflammatory disease

Any infection of the female upper genital tract is considered to be PID; this can include a spectrum of disorders, such as: Endometritis; salpingitis; tubo-ovarian abscess; and pelvic peritonitis (Centers for Disease Control and Prevention, 2010). PID is caused by the ascent of either sexually transmitted pathogens, such as *C. trachomatis* and *Neisseria gonorrhoea,* or normal endogenous vaginal

microorganisms from the endocervix. PID is the most common serious complication of STI in high-income countries (Padian and Washington, 1994). The higher rates of PID seen in younger women have been most commonly attributed to their greater biologic vulnerability, as well as behavioural risk factors that lead to high rates of *C. trachomatis* and other STIs, although insertion of intra-uterine contraceptive devices and some female hygiene practices such as douching are also risks for PID (Igra, 1998, Gray-Swain and Peipert, 2006, Simms *et al.*, 2006, Centers for Disease Control and Prevention, 2010).

An episode of PID may cause symptoms such as lower abdominal pain, fever, unusual vaginal discharge, painful intercourse/urination and abnormal uterine bleeding. However, it is frequently asymptomatic and may remain undiagnosed in many women (Centers for Disease Control and Prevention, 2010). A history of PID may not become evident until serious longer-term sequelae manifest, those sequelae being infertility, ectopic pregnancy and chronic pelvic pain (Padian and Washington, 1994, Gray-Swain and Peipert, 2006). Tubal factor infertility can account for a substantial proportion of female factor infertility, especially in populations with a high prevalence of STIs. The most common cause of tubal factor infertility is PID (Igra, 1998, Dun and Nezhat, 2012). The reported proportion of women who experience infertility after PID varies from 10–40% and approximately 10% of women experience ectopic pregnancy subsequent to PID (Westrom *et al.*, 1992, Pavletic *et al.*, 1999). Overall, increasing severity of PID and repeated episodes of severe disease strongly correlate with higher rates of tubal factor infertility and a lower long-term probability of live birth (Westrom *et al.*, 1992, Lepine *et al.*, 1998).

Ectopic pregnancy

Any pregnancy where an embryo implants outside the endometrial lining of the uterus is considered an ectopic pregnancy. Ectopic pregnancies are inevitably non-viable. Around 1% of all pregnancies are ectopic, most commonly occurring in the fallopian tubes (over 95% of ectopic pregnancies), but also occurring in the cervix, ovaries or abdomen (Chavkin, 1982). If untreated, the condition can lead to life threatening complications through rupture if tubal, with up to 10% of maternal

mortality being attributed to ectopic pregnancies (Doyle *et al.*, 1991, Kamwendo *et al.*, 2000). The increasing use of trans-vaginal ultrasound and quantitative measurement of human chorionic gonadotropin in the last 15 years has led to earlier diagnoses. Earlier diagnosis has allowed for treatment options other than the traditional surgery. Conservative, expectant management is possible and methotrexate (a drug used in cancer treatment) can be used instead of surgery in some women (Mavrelos *et al.*, 2013). Preventing damage to the fallopian tubes reduces future likelihood of repeat ectopic pregnancy and/or infertility (Farquhar, 2005). Due to this consequent effect on fertility (as outlined below), it has even been recommended that women who have experienced more than one ectopic pregnancy should be automatically considered for ART, however, this recommendation was made before non-surgical treatments became relatively common (Skjeldestad *et al.*, 1998).

Ectopic pregnancy is closely associated with infertility and spontaneous abortion, reflecting common pathways and risk factors (Bouyer *et al.*, 2003). A large French case-control study identified the main risk factors and their associated population attributable risk fractions for ectopic pregnancy. They found a history of PID and/or STIs (attributable risk: 0.33, OR: 3.4) and smoking over 20 cigarettes a day (compared with non smokers) (attributable risk: 0.35, OR: 3.9) were the strongest risk factors. The other main risk factors were older age (rates in those aged 35 years or more were more than double those in the age range 25–29 years), prior spontaneous abortions, a history of infertility, and previous use of an intra uterine device (Bouyer *et al.*, 2003). Many other studies have confirmed these risk factors, as well as previous ectopic pregnancy, tubal surgery, documented tubal pathology, and in utero diethylstilbestrol exposure (Ankum *et al.*, 1996, Kamwendo *et al.*, 2000).

6.1.3 Limitations in the interpretation of routinely collected data on pelvic inflammatory disease and ectopic pregnancy

Diagnosis of PID is difficult due to the poly-microbial aetiology, the varying severity of symptoms and non-specificity of symptoms (Haggerty and Ness, 2006).

In general, in the absence of a precise test for PID, a diagnosis is usually based on clinical findings, especially as laparoscopy is difficult to justify for mild cases and cannot confirm some disorders such as endometritis and mild inflammation (Centers for Disease Control and Prevention, 2010). Therefore, diagnosis is very subjective and lacking in both sensitivity and specificity (Peipert *et al.*, 2001, Gaitan *et al.*, 2002, Wiesenfeld and Cates, 2007). In most countries only complicated cases of PID are likely to be hospitalised and the remaining majority of cases are either treated as outpatients or undiagnosed (especially in the case of asymptomatic PID). This PID outpatient treatment policy is recommended in international guidelines (Royal College of Obstetricians and Gynaecologists, 2008, Mol *et al.*, 2010). In the USA, it was estimated that between 75% and 90% of women with PID were treated as outpatients (Centers for Disease Control and Prevention, 2006). According to one Australian study, between 1998 and 2003, just 0.3% of general practice clinical encounters for PID resulted in hospital referral (Chen *et al.*, 2006).

As PID diagnoses are frequently made in the absence of another explanation for symptoms (Gillett, 2014a), and the varying degree of accuracy when PID is diagnosed without a confirmatory test (such as laparoscopy), it is very likely that there are inaccuracies in the levels of diagnosed PID. It is also likely that, as the majority of PID is not diagnosed in hospitals or even diagnosed at all, the trend in hospital diagnosed PID may not reflect the trends in PID diagnosed elsewhere, nor the trend in undiagnosed PID. Changes in clinical practice, subjective diagnosis, and the fact that the majority of PID is not seen in hospitals, bring into question the robustness of the PID data.

Unlike PID, diagnosis of an ectopic pregnancy is not subjective, and historically women presenting with ectopic pregnancy were surgically treated as inpatients, making the monitoring of trends from hospital admissions more accurate. However, advances in diagnosis and medical treatment since the late 1990s may have influenced the admission rates, with earlier detection and modern conservative management resulting in a higher proportion of cases that can be treated as outpatients. The modern management of ectopic pregnancy starts with

the expectant conservative approach and admission is not required. Data on the trends towards increasing treatment of ectopic pregnancy in outpatient settings are conflicting, with Mol *et al.* reporting in the Netherlands that just 5% of ectopic pregnancies were treated as outpatients (Mol *et al.*, 2010). Whereas, in the Washington and Idaho states in the USA, Trabert *et al*. (2011) reported that the proportion of inpatient cases decreased from 45% in the period from 1993–1995 to 27% in the period from 2005–2007. The level of outpatient care in New Zealand is unclear; Morgan *et al.* (2011) provided evidence that historically the vast majority of cases were treated as hospital inpatients. However, more recent estimates based on clinicians' observations suggest that 30–50% of ectopic pregnancies may be being managed as outpatients (Gillett, 2014a).

6.1.4 Trends in routine data on pelvic inflammatory disease and ectopic pregnancy in developed countries

Pelvic inflammatory disease

Studies on the historical trends of PID diagnoses in USA, Norway, and the Netherlands report a consistent decline in hospitalisations for acute PID from the 1970s to the latest data in the mid-2000s (Rolfs *et al.*, 1992, Sorbye *et al.*, 2005, Mol *et al.*, 2010). However, there are no data to suggest declining PID in primary care, which in the USA remained stable during the 1970s and 1980s (Rolfs *et al.*, 1992). It has been hypothesised that the decline in hospitalisations may be due to a changing aetiology in the causation of PID; a lower proportion of PID is being caused by *N. gonorrhoea*, which generally produces more acute symptoms than *C. trachomatis* (Wiesenfeld and Cates, 2007). An alternative explanation would be that this decrease is due to a changing pattern in hospitalisations.

More recent data on PID trends (and also ectopic pregnancy), presented by Bender *et al*. (2011), compared rates of PID hospitals admissions in various countries, including New Zealand. In New Zealand these rates were calculated based on the primary admission diagnosis only (a typical hospital admission in New Zealand generates up to 10 different diagnosis codes, with up to 30 codes allowable). They found the highest rates of PID were in New Zealand, peaking at 193.7 per 100,000

women in 2008. It is important to note that New Zealand's rates are based only on data from three northern regions (Auckland, Bay of Plenty and Waikato), and may, therefore, not be representative of the whole country (Morgan *et al.*, 2011). Denmark (106.0 per 100,000 women in 2004) and Australia (88.8 per 100,000 women in 2007) also had relatively high rates, however, unlike New Zealand, these rates were declining over time. The lowest rates in 2008 were in the Netherlands and Sweden, both being less than 50 per 100,000 women. Contrary to previous evidence, in all study countries apart from New Zealand, the lowest rates were reported in 15–19 year-olds. In New Zealand, this age group has had a dramatic increase in rates since 2005 and had the highest rate of all age groups in 2008 at over 300 per 100,000 women. New Zealand was the only country reporting an overall apparent increase in PID over time (Bender *et al.*, 2011). These country-specific rates were based on population estimates for women aged 15–39 years in each country and the rates were age-standardised to the European standard population.

Māori form a significant proportion of the New Zealand population (14.6% in 2006). In the North Island a greater proportion of the population are Māori, in Northland, the Bay of Islands and the East Coast regions, Māori account for upwards of 25% of the population. In the majority of South Island regions Māori account for less than 10% of the population (Statistics New Zealand, 2007a). This statistic needs consideration when interpreting the published PID data. A summary of statistical evidence for the 'He Kākano: Māori views and experiences of fertility, reproduction and ART' project, reported that for the period 2000–2005 the age-standardised rate of hospitalised PID for Māori was 185.5 per 100,000 women compared with 94.8 for non-Māori (Reynolds and Smith, 2012). This is a near doubling of the risk of PID in Māori compared with non-Māori (RR 1.96, 95% CI 1.84–2.08). This high burden of PID amongst Māori is most likely explained by the significant differences in the levels of diagnosed STIs between European New Zealanders and all other ethnicities. Under half of diagnosed cases of *C. trachomatis* (45%) and *N. gonorrhoea* (42%) in 2011 were amongst European New Zealanders (who make up over 75% of the population) (The Institute of Environmental Science and Research Ltd., 2012). These differences in the burdens of diagnosed

STIs (and PID) may underestimate the underlying differences in the population due to inequitable healthcare access, with lower rates attendance at sexual health clinics by non-European New Zealanders. Further data from Auckland and Northland regions evidenced that, for Māori women receiving infertility treatment in the mid-to-late 1990s, there was a disproportionate burden of tubal factor infertility compared with European women (43% of cases compared with 19%) Reynolds and Smith (2012). This excess burden of tubal factor infertility is possibly a reflection of the much higher burden of PID in Māori. This result not only demonstrates an important disparity between Māori and non-Māori, but would also suggest that the published PID data, being limited to regions with higher proportions of Māori residents, may not necessarily be generalisable to the whole country unless standardised for ethnicity.

Ectopic pregnancy

Historically, the reported incidence of ectopic pregnancy increased during the 1970s and 1980s, thereafter it has declined or remained stable in most developed countries until as recently as the early 2000s (Boufous *et al.*, 2001, Van Den Eeden *et al.*, 2005, Bender *et al.*, 2011, Liu *et al.*, 2012). Data from the Netherlands, Canada and the USA suggest rates again increasing from the mid-2000s (Mol *et al.*, 2010, Trabert *et al.*, 2011, Rekart *et al.*, 2013).

Data from inpatient and outpatient sources for 2005–2007 from the Washington and Idaho states of the USA reveal increasing rates of ectopic pregnancy, reaching relatively high rates of 26.2 per 1,000 pregnancies in 2007 (Trabert *et al.*, 2011). Data from Northern California show an annual rate of 20.7 per 1,000 reported pregnancies during 1997–2000 (Van Den Eeden *et al.*, 2005), with no detectable increase in rates. These data suggest the USA has the highest reported burden of ectopic pregnancy in high-income countries, especially if these data only include the more affluent women with better access to services via their health insurance (which is possible due to the fragmented nature of health systems in the USA).

In Bender *et al.*'s (2011) cross-national study, which did not include the USA, the highest rate of ectopic pregnancy amongst women aged 15–39 years was recorded

by New Zealand at 17.5 per 1,000 live births in 2008. The lowest rate was the Netherlands at 10.1 per 1,000 live births in 2008. Overall rates between 1999 and 2008 were stable in Australia and New Zealand, decreasing in Denmark, but increasing in specific age groups in the Netherlands, Sweden and Switzerland (Bender *et al.*, 2011).

Morgan *et al.* (2011) further analysed the New Zealand data (this was generalised from Waikato, Bay of Plenty and Auckland regions as per Bender *et al*. [2011]), reporting that there was no significant trends across any age group rates for hospital admissions in women aged 15–44 years (median 129 per 100,000 women, 18.8 per 1,000 live births). Why this rate is slightly higher than that reported by Bender *et al.* (2011) is not immediately discernible, as the data were for the same time period and the same regions of New Zealand. However, this could have been a combination of the inclusion by Morgan *et al.* (2011) of women aged 40–44 years and the use of crude rather than age-standardised rates. Age standardising to the older European population would lead to a slight increase from the crude rate to the age-standardised rate. The differences between the two publications are unlikely to be due to inclusion criteria as the author supplied numbers of diagnoses of ectopic pregnancy by age group and year in New Zealand for Bender *et al.*'s 2011 study.

It is again important to consider the generalisability of the regional data in New Zealand. From 2000–2005, Māori population-based rates of ectopic pregnancy were significantly higher than non-Māori in women under the age of 35 years, and for women under the age of 25 years the risk was more than double (Reynolds and Smith, 2012).

6.1.5 Summary

A complex and not fully delineated relationship exists between PID, ectopic pregnancy and tubal factor infertility. Rates of PID and ectopic pregnancy have been investigated in some European countries, and states of the USA, particularly with a view to making ecological comparisons with *C. trachomatis* prevalence and screening policies. Rates have been decreasing since the 1980s, although there is

evidence of recent increases. New Zealand appears to have some of the highest rates of PID and ectopic pregnancy in high-income countries. Furthermore, the issues of PID in relation to ectopic pregnancy and tubal factor infertility are particularly important in addressing health disparities within New Zealand; the evidence strongly suggests that Māori women have a disproportionate burden of PID, ectopic pregnancy and possibly tubal factor infertility.

There is a paucity of national data on infertility, PID and ectopic pregnancy hospitalisations in New Zealand. It is feasible that discharge diagnoses for publicly funded hospital admissions related to these conditions could provide a basis for exploring trends in New Zealand. Investigating the feasibility of using these data is important given the relationship between PID, ectopic pregnancy and future reproductive morbidity and the apparent heightened risk for New Zealand women. The study also provides a frame for the potential New Zealand-wide generalisation of the population-based and clinic-based research in Otago and Southland presented in this thesis (Chapters Three and Four respectively).

However, for all three of these conditions, the underlying levels of disease may not be very well reflected by rates of hospital discharges and the data must, therefore, be interpreted with caution. As previously discussed, hospitalisations for infertility are more likely than the other conditions to be strongly influenced by funding policies and available technologies. Therefore, there is little utility in comparing rates over time or between countries. However, these data could potentially be useful for regional comparisons in a limited time-frame, where the funding and access policies are universally applied, and changes in clinical practice and/or available technology over a short period are not likely.

6.2 Study objectives

This analysis of hospital discharge data addressed the third overall aim for this thesis:

To determine the feasibility of using national hospital discharge data to examine the rates and trends in infertility and markers of tubal factor infertility, and compare those data from Otago and Southland to the national figures.

This was done by analysing the trends over the time period 1988–2009, by age, by deprivation score, by ethnicity and by DHB for hospital discharge codes related to the following:

- Infertility.
- Pelvic inflammatory disease.
- Ectopic pregnancy.

6.3 Methods

6.3.1 Population, data sources and definitions

Population

The study population comprises of all women resident in New Zealand who were aged 15–44 years in any of the years from 1988–2009.

Data source: Denominators for rates

The 2006 population census counts of total resident population in New Zealand and 2006–2009 birth registration data counts of live births grouped by DHB area, five-year age band from 15–44 years, prioritised ethnicity, and NZDep06 decile were used as the denominators for calculating rates. Statistics New Zealand provided these data. For census population data, Statistics New Zealand censors the numbers for groups with counts below five and all counts above five are rounded to base three (the nearest whole number divisible by three). Therefore, adding together the numbers in these groups does not give the precise number of the whole population, but as the counts are relatively large, any imprecision introduced is very minimal. The 2006 census data were chosen as earlier data did not record ethnicity as well, and this census was within the range of the numerator data dates, furthermore, between census years, data provided by Statistics New Zealand for population counts are extrapolations of the previous census. These extrapolations do not provide the level of detail required to calculate rates for this analysis.

Data source: Numerators for rates

The Ministry of Health maintains a number of national data collections, which health information to support decision-making in policy development, funding and at the point of care. These datasets can be accessed for research purposes upon request. One of these collections, the National Minimum Dataset, contains records of all public (since 1988) and private (since 1997) hospital discharges in New Zealand for all publicly funded cases (Ministry of Health, 2012). Those cases admitted to hospital, but privately funded, were not included in the National Minimum dataset. In New Zealand, all patients who spend longer than three hours at a hospital, even in the emergency or outpatients departments, have to be admitted to the hospital as an inpatient, all of these patients have a unique discharge record for each hospital discharge within the National Minimum Dataset.

The Ministry of Health produced for this study an extract from the National Minimum Dataset including NHI number, date of birth, the hospital providing care, date of admission, up to 30 diagnosis codes and up to 30 procedure codes per discharge record. Diagnosis codes associated with each hospital discharge were recorded in the International Classification of Diseases (ICD)-9 and ICD-10 formats, which include infertility, PID and ectopic pregnancies. All discharge records dated from 1988–2009 that contained at least one primary (the first diagnosis field and primary reason for hospital admission) or secondary diagnosis code (any other diagnosis recorded that was not identified as the primary reason for admission) pertaining to infertility, PID or ectopic pregnancy were extracted. Data were then linked in-house by the Ministry of Health, via the NHI number for each record, to ethnicity and the domicile area to which the patient's residential address belongs (see Section 4.3.3, page 148, for further explanation of NHI numbers and related data).

The Ministry of Health then anonymised the data by replacing NHI number with an encrypted number. Using Microsoft Access, the domicile area was linked to its deprivation decile score for the area in 2006, as derived from the 2006 census (NZDep06) (see Section 3.3.14, page 86, for a more detailed explanation of the New Zealand Deprivation Index).

Limitations of the National Minimum Dataset

The National Minimum Dataset excludes cases that are managed in completely privately funded settings, within emergency departments but not admitted, in outpatient clinics or in primary care. The proportion of cases managed outside public hospital settings, and whether this has changed over time, is unknown. This issue is especially relevant when considering PID and infertility treatment. Duplicated admissions are common in the National Minimum Dataset, these generally arise when a patient is transferred between departments, resulting in a 'discharge' (and it associated data record) from the first department and then the patient is re-admitted in the next department, which also generates a discharge when the patient leaves this department/the hospital. However, it is likely that most repeat admissions were identified and removed from the data set during data cleaning. Repeat admissions for the same condition over time are also extremely common; these could not be completely excluded.

Specific definitions for infertility, pelvic inflammatory disease and ectopic pregnancy diagnoses

ICD version 9-CMA-II (ICD-9) and version 10-AM-V1 (ICD-10) codes for reproductive tract conditions (female infertility from any cause, PID and ectopic pregnancy) were selected in consultation with Ministry of Health data analysts and Professor Wayne Gillett (who is a gynaecologist). ICD-9 codes were in use up to and including 1999; thereafter clinical codes were in ICD-10 format. Specifically, for infertility this was any ICD-9 628.0 or 628.2–682.9 codes, for PID any 614–616 codes, and for ectopic pregnancy any 633 code. Further details of exact ICD-9 codes are presented in Table 6.1. The Ministry of Health provided all data in ICD-9 coding, and from 2000–2009 this was an automated process mapping from ICD-10 coding. Precise details of how this was done, however, were not made available.

Summary yes/no binary variables were provided by the Ministry of Health for infertility, PID and ectopic pregnancy where the variable was coded as a 'yes' if in any of the up to 30 diagnosis codes there was an ICD-9 code for that condition.

Table 6.1: ICD-9 codes used to identify hospital admissions for PID, ectopic pregnancy and infertility

Female infertility
628.0 Infertility, female, associated with anovulation
628.2 Infertility, female, of tubal origin
628.3 Infertility, female, of uterine origin
628.4 Infertility, female, of cervical or vaginal origin
628.8 Infertility, female, of other specified origin
628.9 Infertility, female, of unspecified origin
Inflammatory disease of female pelvic organs
614 Inflammatory disease of ovary fallopian tube pelvic cellular tissue and peritoneum
614.0 Acute salpingitis and oophoritis
614.1 Chronic salpingitis and oophoritis
614.2 Salpingitis and oophoritis not specified as acute, subacute, or chronic
614.3 Acute parametritis and pelvic cellulitis
614.4 Chronic or unspecified parametritis and pelvic cellulitis
614.5 Acute or unspecified pelvic peritonitis, female
614.6 Pelvic peritoneal adhesions, female (postoperative) (postinfection)
614.7 Other chronic pelvic peritonitis, female
614.8 Other specified inflammatory disease
614.9 Unspecified inflammatory disease
615 Inflammatory diseases of uterus except cervix
615.0 Acute inflammatory diseases of uterus, except cervix
615.1 Chronic inflammatory diseases of uterus, except cervix
615.9 Unspecified inflammatory disease of uterus
Ectopic pregnancy
633.0 Abdominal pregnancy
633.00 … without intrauterine pregnancy
633.01 … with intrauterine pregnancy
633.1 Tubal pregnancy
633.0 Abdominal pregnancy
633.00 … without intrauterine pregnancy
633.01 … with intrauterine pregnancy
Ectopic pregnancy
633.1 Tubal pregnancy
633.10 … without intrauterine pregnancy
633.11 … with intrauterine pregnancy

Table 6.1 ***continued***

633.2 Ovarian pregnancy
633.20 … without intrauterine pregnancy
633.21 … with intrauterine pregnancy
633.8 Other ectopic pregnancy
633.80 … without intrauterine pregnancy
633.81 … with intrauterine pregnancy
633.9 Unspecified ectopic pregnancy
633.90 … without intrauterine pregnancy
633.91 … with intrauterine pregnancy

Modification and creation of variables

Age

Age at admission was calculated by deducting admission date from date of birth and dividing by 365.25. Age was then grouped by five-year age bands: 15 up to but not including 20; 20 to less than 25; 25 to less than 30; 30 to less than 35; 35 to less than 40; and 40 to less than 45 years. This is in line with census groupings where if a person turns 40 years old the day *after* census they would be in the 35–39 year age group. For simplicity these age groups are herein referred to as age 15–19, 20–24, 25–29, 30–34, 35–39 and 40–44 years.

Ethnicity

Issues in the collection, coding and reporting of ethnicity data were previously outlined in Section 3.3.13 on page 84. Live births from birth registration data has the self-specified Other ethnicity response 'New Zealander' coded in the 'European' category, as does the numerator data from the National Minimum Dataset (Ministry of Health, 2009). Therefore, to avoid numerator denominator differences the most prudent approach regarding ethnicity classification was to group the census 'New Zealander' responses with 'European' and not the default 'Other' grouping that has been commonly used in the census datasets. Multiple ethnicity responses were coded to a single ethnicity for analysis using the prioritising method previously outlined, where the highest priority for multiple ethnicity

responses was given to any report of Māori ethnicity, followed by Pacific Peoples, Asian, Other ethnicity, and if the only ethnicity reported was European, then European ethnicity was assigned.

Additional PID diagnosis variables

A yes/no binary variable for PID being the primary diagnosis (so limited to PID in only the first diagnosis field only) was generated. As it is recognised that a diagnosis of PID is subjective and sometimes made with little evidence, a further variable was made categorising PID by the level of evidence for PID that was available within the discharge record. Based on the Centers for Disease Control and Prevention (2010) PID diagnosis guidelines and the analysis of the accuracy of clinical and laparoscopic findings by other researchers (Sellors *et al.*, 1991, Paavonen and Lehtinen, 1996, Gaitan *et al.*, 2002), the following mutually exclusive groupings for evidenced level of certainty in the PID diagnosis were created:

1. 'PID, no further evidence'

2. 'PID with specific clinical evidence'

   - Venereal disease at any site (ICD-9 diagnosis categories 091, 098, 099 and 131), as PID has poly-microbial aetiology; or
   - Fever (ICD-9 diagnosis codes 780.60 and 780.61) and any of Abdominal pain, tenderness, swelling (ICD-9 diagnosis codes 789.0, 789.6 and 789.3), as these are all non-specific clinical symptoms of PID.

3. 'PID, confirmed'

   - Laparoscopy (procedure code 5421), as this would suggest that PID was definitively ascertained; or
   - Any acute PID (614.0–614.2 codes) and an ultrasound or CT scan (procedure codes 8876, 8879 and 8801), as these are the recommended procedures for confirming acute PID.

6.3.2 Data cleaning

Data were imported into STATA 12.1/IC for cleaning and preparation.

Discharge records were excluded if:

- Male sex was identified[1].
- Age at admission was less than 15 years or 45 years and above.
- Not resident in New Zealand.
- Identified as a duplicate.

Discharge records were considered duplicates in any of the following three scenarios:

1. Same admission date duplicates

Encrypted NHI number (unique for any individual woman) and admission date were not unique. In this scenario, any additional diagnosis codes and any missing demographic data from duplicates on the same admission date were merged into the first record, and only the first record for a given encrypted NHI number and admission date combination was kept. If, when merging records there was more than one ethnicity reported, ethnicity was prioritised as detailed earlier.

2. Repeated episodes of infertility or PID

An individual woman had an episode of infertility or PID (within any of the up to 30 diagnosis codes provided) after the first episode of hospitalisation for this condition. In this scenario, any missing demographic data were merged into the first record, prioritising ethnicity, and all repeated admissions following this condition were deleted.

3. Repeated admission for the same ectopic pregnancy

An individual woman had a second ectopic pregnancy discharge (within any of the up to 30 diagnosis codes provided) within an arbitrarily defined period of 42 days since a previous ectopic pregnancy discharge. In this scenario, missing demographic data were merged into the first occurrence, prioritising ethnicity, and then only the first occurrence of the diagnosis within the 42-day period was kept.

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[1] Excluded based on recommendation of the Ministry of Health, who confirmed the cases were male and the discharge diagnosis codes were in error.

6.3.3 Statistical analyses

All data were analysed in STATA 12.1/SE. Adobe Photoshop 6.0 was used to produce map images.

Rates for infertility, pelvic inflammatory disease and ectopic pregnancy

The annual age-standardised rates from 1988–2009 for New Zealand, the Otago/Southland (Southern) DHBs, the remaining South Island region and the North Island (yearly rate 1988–2009, 3-year moving average 1993–2009) were calculated for infertility, PID and ectopic pregnancy. The age-standardised rates were calculated by direct age-standardisation (Webb *et al.*, 2005b), the 2006 New Zealand female population aged 15–44 years (in five-year age bands) was used as the standard population. Overall and age-specific rates per 100,000 women were then calculated, limited to data for the five-year period from 2005–2009. DHB, ethnicity and NZDep06-specific hospital discharge age-standardised rates were calculated per 100,000 women. The ethnicity-specific analysis was then adjusted due to extremely high admissions amongst the ethnicity 'Other'. This was most likely due to a mismatch in the numerator and denominator data arising from confusion around the classification of the 'New Zealander' response. As it was not possible to further examine or rectify this issue, 'Other' and 'European' were combined for further analyses.

The rates of ectopic pregnancies were also calculated per 1,000 live births. Less frequently used denominators for ectopic pregnancy rates, such as the number of all known pregnancies (live births, miscarriages, and terminations) and the number of all viable pregnancies (Salman and Irvine, 2008), were not available in New Zealand in the level of detail required for this analysis. The number of women of reproductive capability is not affected by trends in miscarriages and terminations, but it is influenced by the fertility rates and contraceptive practices. Therefore, expressing the ectopic pregnancy rate per 1,000 live births was the most suitable and comparable method.

Risk model for infertility, pelvic inflammatory disease and ectopic pregnancy

To analyse overall risk, and in particular investigate differences by DHB, adjusted incidence rate ratios (IRR) were calculated using Poisson regression, with the population strata denominator as an exposure. For infertility and ectopic pregnancies the model was repeated with births as the exposure. Ethnicity and age group were added with an interaction term and the models compared with and without the interaction terms using likelihood ratio tests. NZDep06 was fitted as a linear term and a quadratic term, and the statistical significance calculated using Wald tests. Each parameter in the model was also checked for overall significance using Wald tests.

The three final models, one each for infertility, PID and ectopic pregnancy, were tested for over dispersion using negative binomial regression and checking the alpha statistics for significance. The models were also examined for zero-inflation using zero-inflated Poisson models.

6.4 Results

6.4.1 Eligible cases

Figure 6.2 details the data cleaning process.

The Ministry of Health provided a total of 144,001 cases from the National Minimum Dataset. However, these cases included many that did not meet the case definition, as the extract included all diagnoses for the ICD category 'Inflammatory Disease of the female pelvic organs 614–616'. Those cases where there was only an ICD-9 616 code (inflammatory disease of cervix, vagina and vulva) did not meet the case definition (as this does not constitute a PID diagnosis). Furthermore, there were some cases that did not meet the other eligibility criteria for gender, date of admission, age and residency status. After removing all of these cases there were 88,318 cases remaining. A small number of duplicate admissions for the same patient and date were found, probably due to being admitted in an emergency department then being technically discharged and re-admitted to another hospital department.

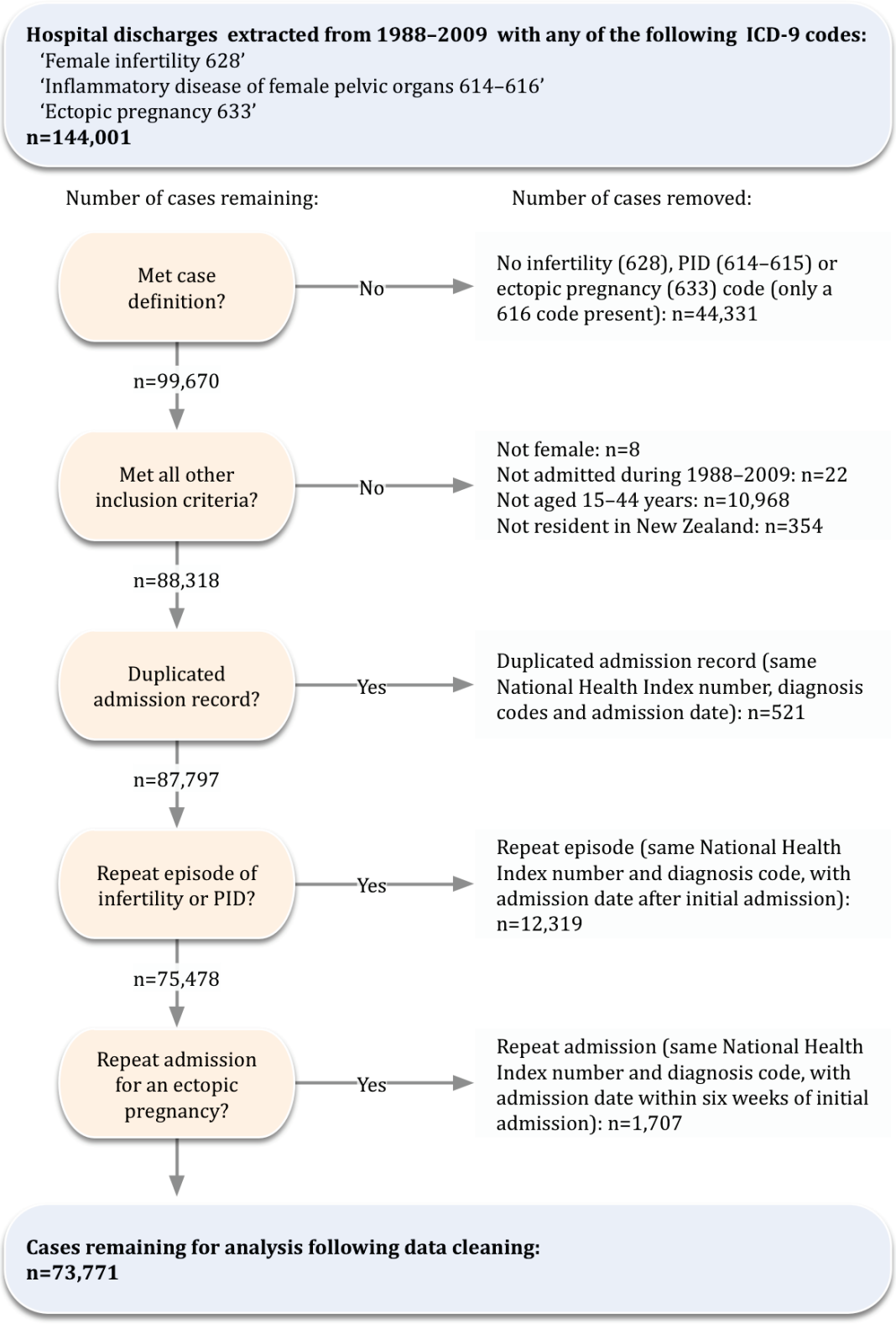


Figure 6.2: Flow chart of the hospital discharge data cleaning process

There were a larger number of cases removed due to being re-admissions for either the likely same episode of disease (for ectopic pregnancy) or recurrences of previous infertility and/or PID. Data cleaning resulted in a total of 73,771 eligible cases for analysis, some of which qualified with more than one of the three conditions of interest (refer to Figure 6.3).

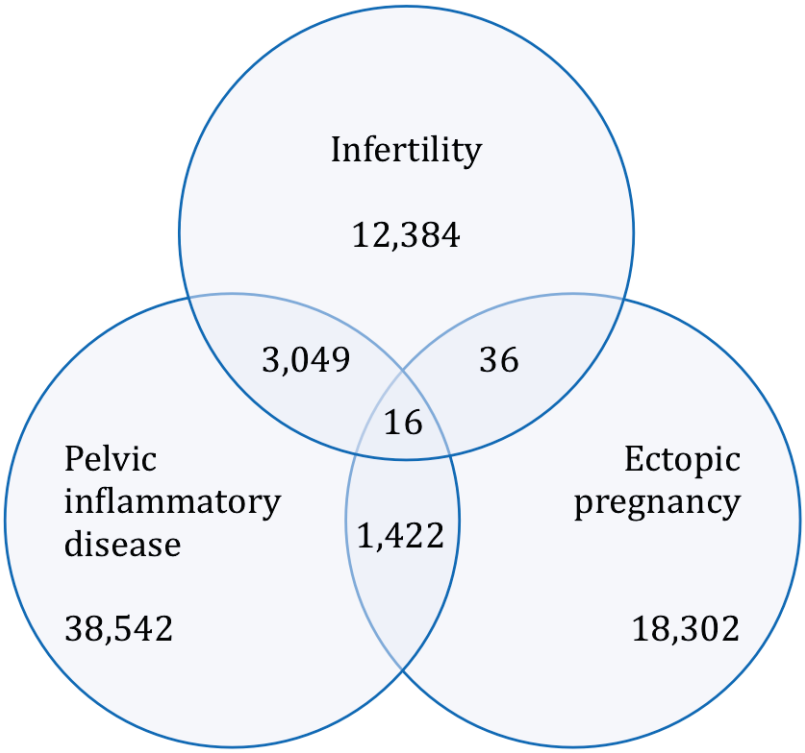


Figure 6.3: Numbers of cases for each combination of diagnoses amongst the 73,771 eligible cases

6.4.2 Rates and patterns of infertility

Overall there were 15,485 cases of infertility during the full study period of 1988–2009, and 2,766 cases when looking at the most recent five-year period ending in 2009.

Time trends in infertility from 1988–2009

The age-standardised rates for publicly funded infertility hospital admissions in all New Zealand were steady throughout the 1990s, and then decreased from the early 2000s (refer to Figure 6.4). The most recent data show the rates have

increased slightly in 2009 to an age-standardised rate of 78.9 per 100,000 women. In the early 1990s Southern has had the highest age-standardised rates; double that of the North Island. Southern DHB's age-standardised rates have, however, declined substantially throughout most of the time period. Age-standardised rates for the rest of the South Island also declined throughout most of the time period, and the North Island pattern was very similar to that seen for all of New Zealand.

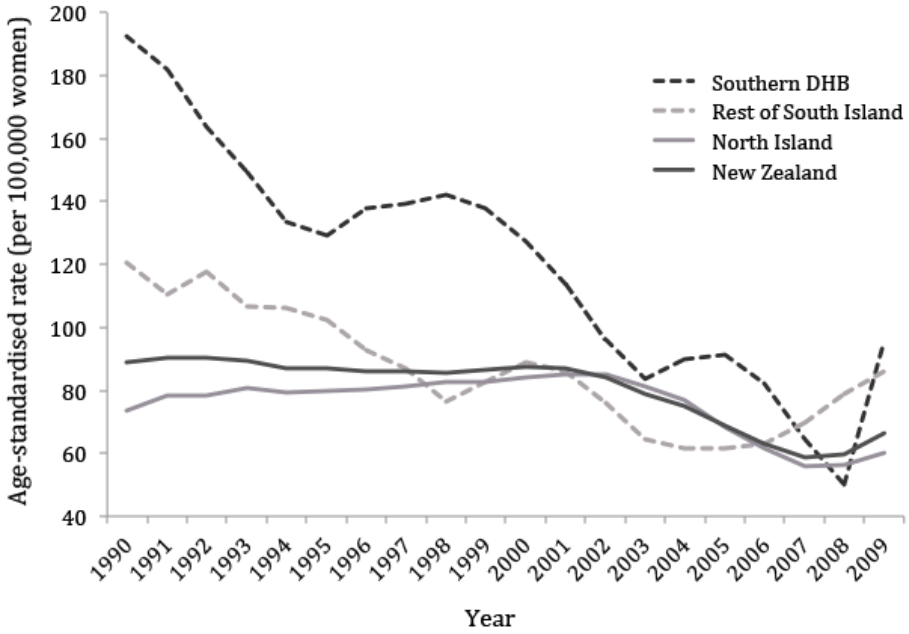


Figure 6.4: Age-standardised rates of publicly funded hospitalisations for infertility in women aged 15–44 years, 3-year moving average 1990–2009

Infertility by district health board from 2005–2009

Overall, the average annual age-standardised rate from 2005–2009 for infertility was 63.2 per 100,000 women. Generally higher age-standardised rates of infertility diagnoses were seen in the South Island, apart from the Canterbury DHB (refer to Figure 6.5 overleaf). Tables with specific age-standardised rates by DHB are in Appendix L on page 355.

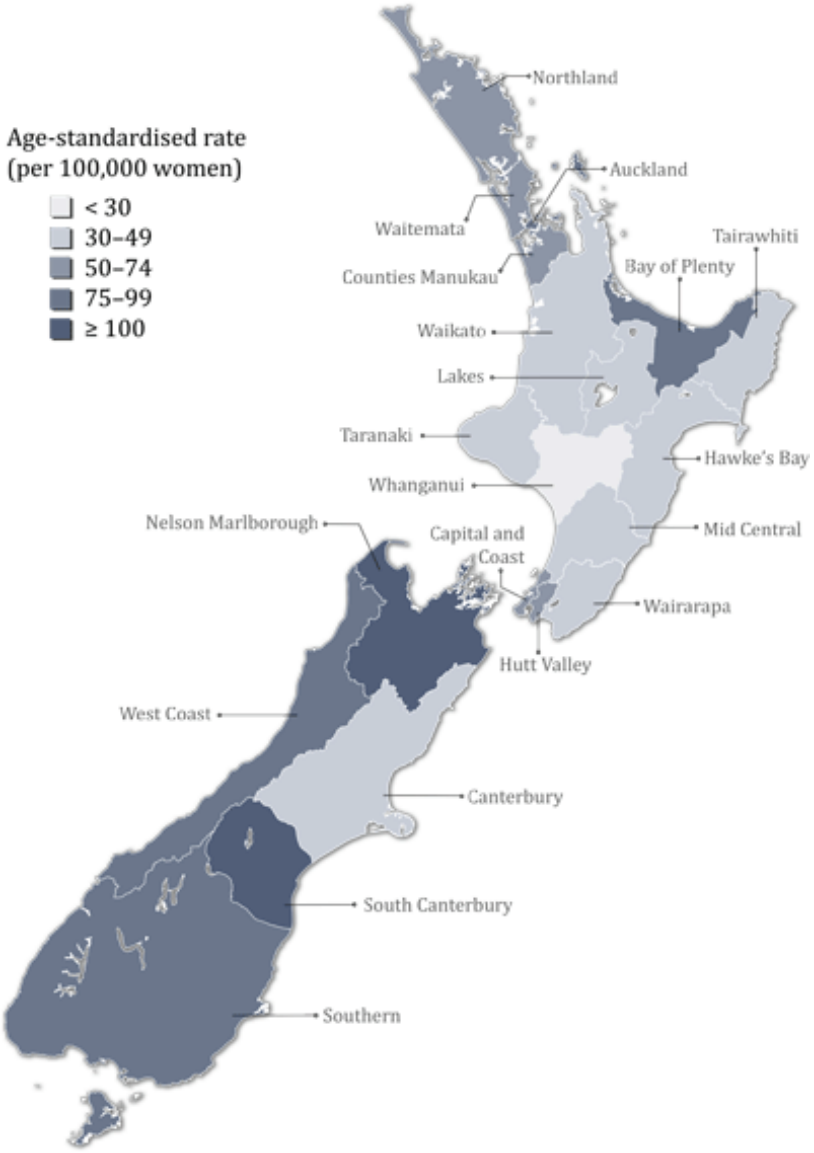


Figure 6.5: Age-standardised rates by DHB of publicly funded hospitalisations for infertility in women aged 15–44 years (average for 2005–2009)

Age, ethnicity and deprivation-specific rates of infertility from 2005–2009

Table 6.2 shows the age-standardised rates of infertility from 2005–2009. The rate climbed with age to peak in the 30–34 year age group, possibly a combination of the increasing risk of infertility with age and the increased fertility between ages 25 and 34.

Table 6.2: Age-specific rates of publicly funded hospitalisations for infertility (average for 2005–2009)

Age group (years)	Rate per 100,000 women	(95% CI)
15–19	1.5	(0.7–2.7)
20–24	21.9	(18.6–25.7)
25–29	75.9	(69.2–83.0)
30–34	134.5	(126.3–143.2)
35–39	118.6	(111.1–126.4)
40–44	25.9	(22.5–29.7)

Table 6.3 shows that the age-standardised rates were similar for women of European/Other and Pacific ethnicities, but substantially lower in Māori.

Table 6.3: Age-standardised rates of publicly funded hospitalisations for infertility by ethnic group in women aged 15–44 years (average for 2005–2009)

Ethnic group	Rate per 100,000 women	(95% CI)
European and Other	66.5	(60.0–73.7)
Māori	40.0	(29.8–52.6)
Pacific	64.9	(44.9–90.8)
Asian	87.9	(70.1–108.8)

Table 6.4 (overleaf) shows the age-standardised rate for publicly funded infertility admissions by deprivation decile. There was an increased rate in deprivation deciles 5–9. This may reflect increased fertility in the mid-to-high deprivation women, or increased infertility in these groups, or a different balance in the proportion that received publicly funded versus privately funded care.

Table 6.4: Age-standardised rates of infertility by deprivation in women aged 15–44 years (average for 2005–2009)

NZDep06 decile*	Rate per 100,000 women	(95% CI)
1	48.4	(34.2–66.6)
2	56.5	(41.6–75.1)
3	57.7	(43.1–75.9)
4	52.5	(38.6–69.9)
5	68.6	(52.4–88.2)
6	64.9	(49.4–83.7)
7	71.9	(55.4–91.7)
8	82.7	(64.8–104.0)
9	73.1	(56.2–93.3)
10	50.7	(36.7–68.1)

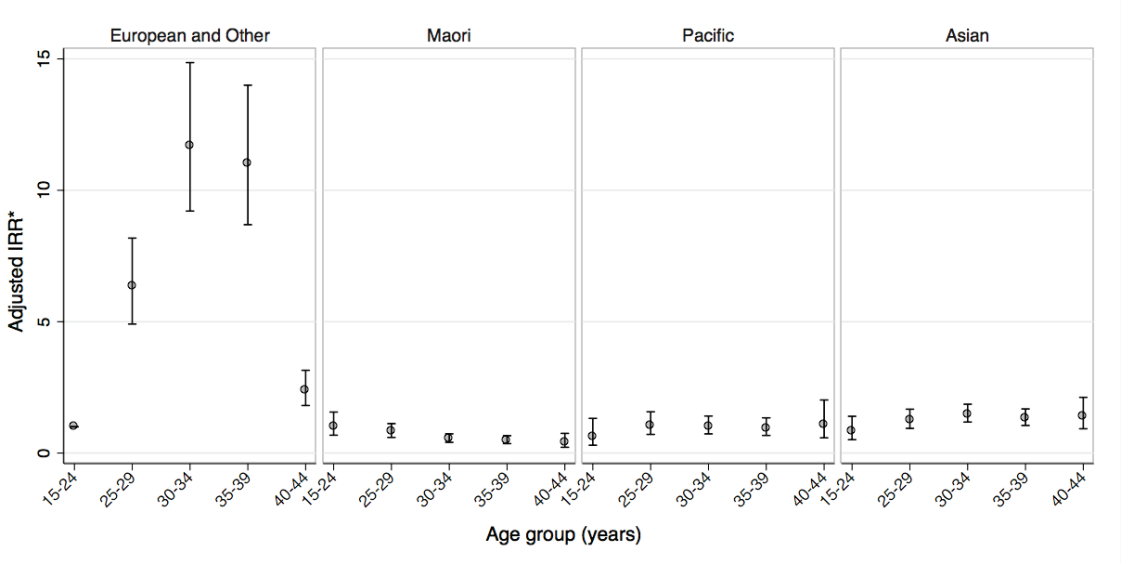
* *Where decile 1 is the population living in the 10% least deprived areas and decile 10 is the 10% most deprived.*

Infertility risk from 2005–2009

Due to low rates of infertility in the youngest two age groups, these groups were combined for Poisson modelling. There was a statistically significant interaction between age and ethnicity (likelihood ratio test p=0.023). Deprivation decile was significant as a linear term and as a quadratic term (Wald tests both p<0.05). The effect of area was also highly significant (p<0.001). There was significant over-dispersion (negative binomial regression alpha statistic p<0.001). So, the final model was constructed using negative binomial regression rather than Poisson regression. Checking for zero-inflation led to an unstable model. Refer to Appendix M from page 359 for the table displaying the final results for the model.

The North Island had an adjusted IRR for infertility admissions of 0.67 (95% CI 0.58–0.79) compared with Southern DHB. There was a statistically significant correlation between increasing deprivation and increasing IRRs for infertility, this association was non-linear (as shown previously in Table 6.4).

The patterns by age and ethnicity varied (refer to Figure 6.6). There was a steep increase in the IRRs by age for European and Other ethnicity, with IRRs above 10 for age groups 30–34 and 35–39 years when compared with 15–24 year-olds. Māori, Pacific and Asian ethnicities had adjusted IRRs that were much lower than that for European and Other ethnicity. For Māori women, the IRR unexpectedly decreased with age.



* *Adjusted for deprivation and geographical area.*

Figure 6.6: Adjusted* IRRs (and 95% CIs) for infertility by age and ethnic group

6.4.3 Rates and patterns of pelvic inflammatory disease

Overall, there were 43,049 cases of PID during the full study period of 1988–2009 and 12,245 cases when looking in the most recent five-year period (2005–2009). Of these, there were 8,497 (19.7%) cases during the full period that qualified as a confirmed case (cases that had other specific clinical evidence) and very few cases with clinical evidence (1,682, 3.9%). Therefore, there were too few cases in the clinical evidence category to continue analysing. As such, the remaining analysis focussed on all primary and secondary diagnoses, primary diagnoses only and confirmed diagnoses only.

In just under half of all primary and secondary PID (45.3%) and confirmed primary and secondary PID cases (48.8%), the primary diagnosis for hospital admission was PID. The other main categories for the primary diagnosis in conjunction with secondary diagnosis of PID are shown in Table 6.5. The main differences for the primary reason for hospital admission in secondary PID cases were regarding admission for diagnoses of endometriosis and infertility. Endometriosis and infertility diagnoses were twice as likely for confirmed cases of PID rather than all diagnoses of PID. Higher proportions of STI and pregnancy related admissions, particularly puerperal infection, were seen in all diagnoses of secondary PID, these diagnoses were minimal for confirmed PID.

Table 6.5: Primary diagnoses in those with a hospital admission for PID

	All primary and secondary diagnoses		Confirmed diagnoses	
Primary diagnosis	**N**	**(%)**	**N**	**(%)**
PID	19,488	(45.3)	4,144	(48.8)
STI	1,073	(2.5)	90	(1.1)
Cancer of genitourinary organs	1,241	(2.9)	162	(1.9)
Ovarian disorder	1,143	(2.7)	351	(4.1)
Menstrual disorder	1,600	(3.7)	371	(4.4)
Endometriosis	2,638	(6.1)	1,020	(12.0)
Other conditions of genitourinary organs	1,999	(4.6)	508	(6.0)
Infertility	1,422	(3.3)	743	(8.7)
Miscarriage/abortion	2,018	(4.7)	84	(1.0)
Ectopic pregnancy	1,525	(3.5)	473	(5.6)
Puerperal infection	2,192	(5.1)	8	(0.1)
C-section or uterine abnormality during pregnancy	1,387	(3.2)	4	(0.1)
Other pregnancy related	2,804	(6.5)	35	(0.4)
Abdominal pain/swelling	524	(1.2)	201	(2.4)
Appendicitis	520	(1.2)	120	(1.4)
Other	1,475	(3.4)	183	(2.2)
Total	43,049		8,497	

Time trends in pelvic inflammatory disease admissions from 1988–2009

Overall, for all hospital admissions where PID was the primary or secondary diagnosis there has been a steady and substantial increase in the age-standardised rate from 196.3 per 100,000 women in 1988 to 278.7 per 100,000 women in 2009 (refer to Figure 6.7 overleaf). This trend was seen in all areas, apart from Southern DHB, where the rate decreased slightly. Since 2000, rates in the Southern DHB have been lower than the rest of New Zealand; in 2009 rates in the rest of New Zealand were 60% higher than in Southern DHB.

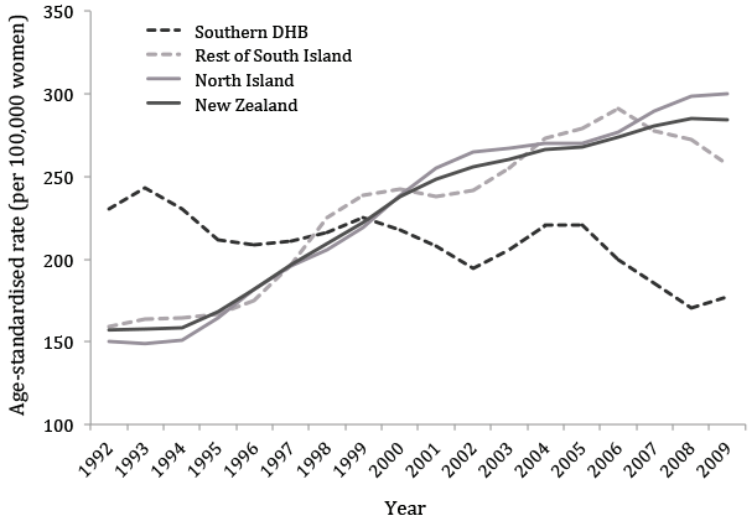
A different pattern is seen when looking at primary diagnoses only. Age-standardised rates steadily decreased up to the mid-2000s, when this decrease plateaued for all areas apart from Southern DHB. In 2009, the age-standardised rate of primary PID diagnoses in New Zealand was 90.7 per 100,000 women, with Southern DHB having a much lower rate than all other areas.

Confirmed PID rates in all areas climbed steeply to peak at 96.0 per 100,000 women in 1998 and then declined steeply to 30.9 per 100,000 women in 2009. Contrary to patterns seen for the other categories of PID, for confirmed diagnoses, age-standardised rates in the South Island were higher than the North Island.

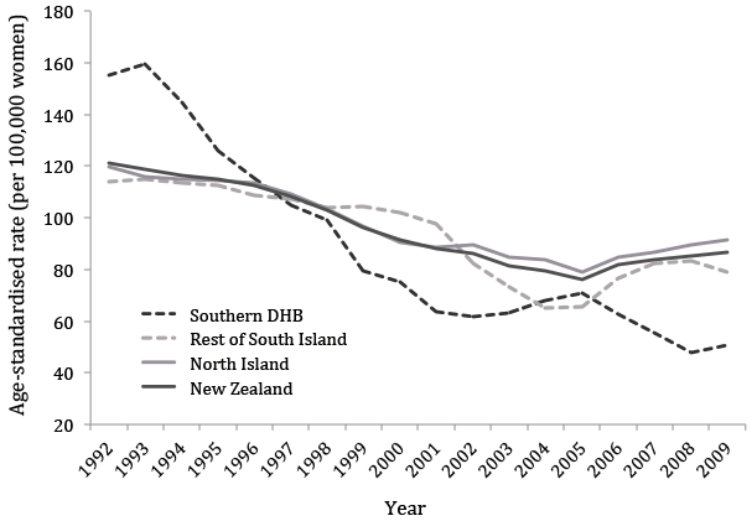
Pelvic inflammatory disease by district health board from 2005–2009

Overall, the average annual rates from 2005–2009 of all primary and secondary PID diagnoses, primary diagnoses only, and confirmed diagnoses only were 279.6, 84.7 and 27.7 per 100,000 women respectively. There was significant variation in the age-standardised rates at the DHB level, with North Island DHBs generally having higher age-standardised rates for all primary and secondary diagnoses and primary diagnoses only of PID than South Island DHBs (refer to Figure 6.8 on page 237). Tables with the age-standardised rates by DHB are in Appendix L on page 356.

(A) All primary and secondary diagnoses



(B) Primary diagnoses only



(C) Confirmed diagnoses only

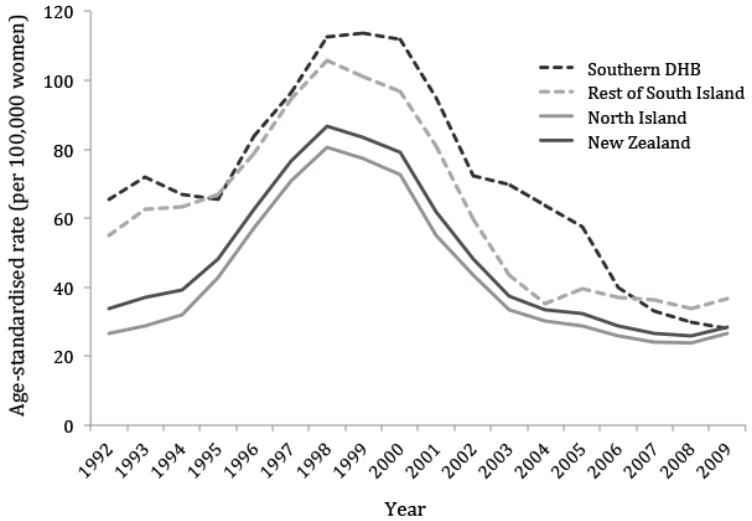
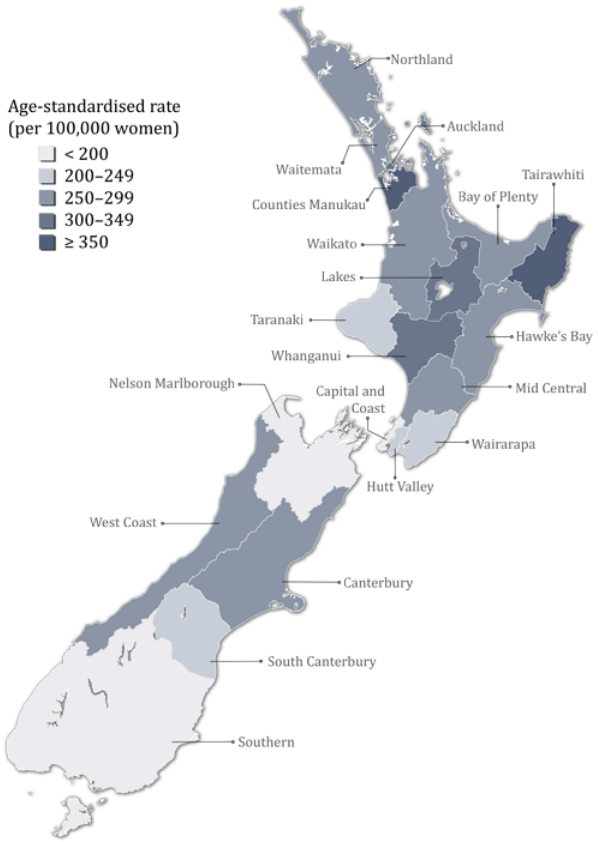
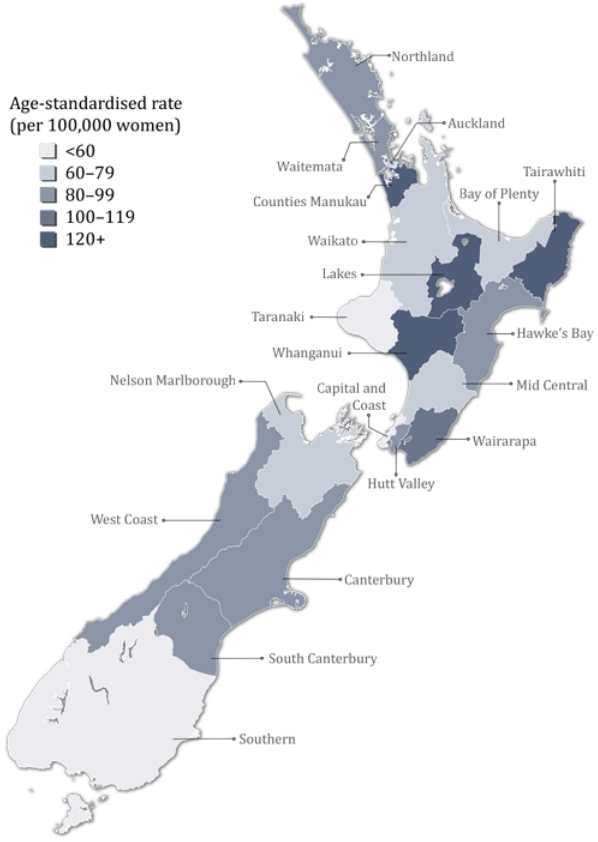


Figure 6.7: Age-standardised rates of publicly funded hospitalisations for PID amongst women aged 15–44 years, 3-year moving average 1988–2009

(A) All primary and secondary diagnoses



(B) Primary diagnoses only



(C) Confirmed diagnoses only

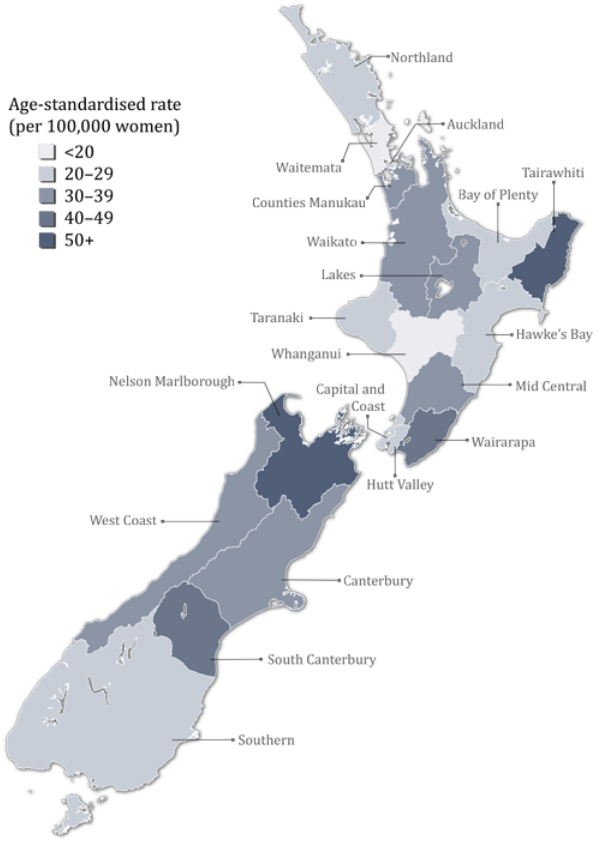


Figure 6.8: Age-standardised rates of publicly funded hospitalisations for PID by DHB in women aged 15–44 years (average for 2005–2009)

Age, ethnicity, and deprivation-specific rates of pelvic inflammatory disease from 2005–2009

Table 6.6 shows the age-specific rates of PID during 2005–2009. The highest rates for all primary and secondary diagnoses and primary diagnoses of PID were in women under the age of 30 years. However, the highest rates of confirmed PID were for women aged 30–39 years.

Table 6.6: Age-specific rates of publicly funded hospitalisations for PID (average for 2005–2009)

Age group (years)	Rate per 100,000 women (95% CI)		
	All primary and secondary PID	Primary diagnoses only	Confirmed diagnoses only
15–19	268.4 (256.7–280.5)	114.8 (107.2–122.8)	20.2 (17.1–23.7)
20–24	344.8 (331.0–359.1)	115.4 (107.5–123.8)	26.8 (23.0–31.0)
25–29	330.3 (316.2–344.8)	91.5 (84.3–99.5)	27.5 (23.5–31.9)
30–34	302.0 (289.5–314.9)	67.4 (61.6–73.6)	32.3 (28.3–36.7)
35–39	273.4 (262.0–285.1)	68.6 (63.0–74.6)	32.4 (28.6–36.6)
40–44	182.3 (173.2–191.8)	57.7 (52.6–63.2)	26.5 (23.1–30.3)

Table 6.7 shows the age-standardised rates of PID by ethnicity during 2005–2009. For all categories of PID diagnosis, age-standardised rates amongst Māori were close to double those of European and Other ethnicity. Pacific people had the highest levels of PID, with all primary and secondary diagnoses being almost three times that of the European and Other age-standardised rates. The Asian ethnic group had the lowest levels of PID.

Table 6.8 shows the age-standardised rates of PID by deprivation decile during 2005–2009. Higher age-standardised rates of PID were seen with increasing deprivation, those in the 10% most deprived category (decile 1) had between two and four times the age-standardised rates of PID when compared with those in the 10% least deprived category (decile 10).

Table 6.7: Age-standardised rates of publicly funded hospitalisations for PID by ethnic group in women aged 15–44 years (average for 2005–2009)

Ethnic group	Rate per 100,000 women (95% CI)		
	All primary and secondary PID	Primary diagnoses only	Confirmed diagnoses only
European and Other	236.0 (223.2–249.3)	74.2 (67.1–81.9)	26.4 (22.2–31.1)
Māori	433.6 (399.4–470.0)	145.8 (126.2–167.5)	41.7 (31.4–54.4)
Pacific	616.8 (552.2–686.8)	159.7 (127.7–197.3)	43.6 (27.4–65.8)
Asian	200.7 (173.6–230.9)	44.0 (31.9–59.2)	16.2 (9.2–26.5)

Table 6.8: Age-standardised rates of publicly funded hospitalisations for PID by deprivation in women aged 15–44 years (average for 2005–2009)

NZDep06 decile*	Rate per 100,000 women (95% CI)		
	All primary and secondary PID	Primary diagnoses only	Confirmed diagnoses only
1	160.1 (132.4–191.9)	44.2 (30.2–62.4)	19.9 (11.2–32.8)
2	197.1 (167.3–230.8)	55.9 (40.5–75.1)	16.6 (8.9–28.3)
3	168.5 (142.0–198.5)	52.9 (38.4–71.0)	18.1 (10.3–29.7)
4	199.1 (170.1–231.6)	60.6 (45.0–79.9)	20.9 (12.2–33.2)
5	238.4 (206.9–273.4)	67.5 (51.2–87.4)	27.0 (17.2–40.4)
6	238.1 (207.2–272.3)	67.5 (51.4–86.9)	24.2 (15.1–36.9)
7	299.6 (264.7–337.8)	94.9 75.8–117.5)	31.4 (20.8–45.5)
8	341.8 (304.7–382.1)	105.7 (85.5–129.1)	31.1 (20.5–45.0)
9	422.7 (381.8–466.7)	127.4 (105.5–152.4)	44.4 (31.6–60.4)
10	473.0 (429.6–519.6)	154.3 (129.9–181.9)	42.4 (29.9–58.4)

* *Where decile 1 is the population living in the 10% least deprived areas and decile 10 is the 10% most deprived.*

Pelvic inflammatory disease risk from 2005–2009

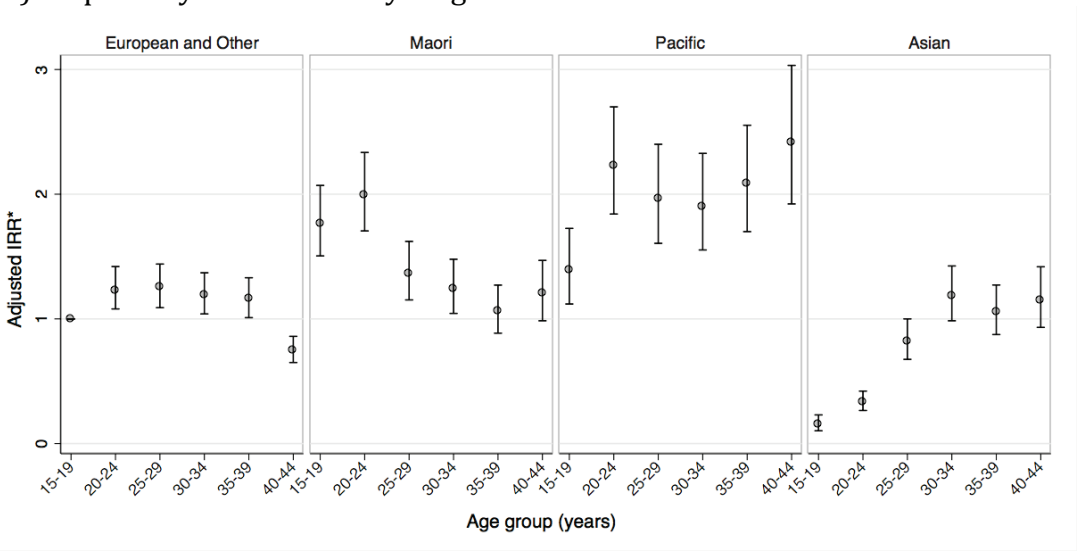
A model was generated for each of the three PID categories: All primary and secondary diagnoses; primary diagnoses only; and confirmed diagnoses only. There were statistically significant interactions between age and ethnicity for all three models (all $p<0.001$). Deprivation decile was added as a linear term, as the quadratic term was not significant ($p=0.424$, 0.135 and 0.334 for the all diagnoses, primary diagnoses and confirmed diagnoses models respectively). All independent variables were highly significant for all three models (all $p<0.001$). The models for all primary and secondary diagnoses and primary diagnoses only had significant over-dispersion (negative binomial regression alpha statistic $p<0.001$ and 0.003 respectively). So, for these two models, the final model was constructed using negative binomial regression rather than Poisson regression. The model for confirmed diagnoses did not have significant over-dispersion (alpha statistic $p=0.298$). Checking for zero-inflation led to unstable models. Refer to Appendix M on pages 361–363 for tables displaying the final results for the models.

For both all primary and secondary diagnoses and primary diagnoses only, the adjusted IRR was 50% higher in both the rest of the South Island and the North Island when compared with the Southern DHB ($p<0.001$ for both models). For confirmed diagnoses only there was no statistically significant difference between Southern DHB and the North Island, however, the rest of the South Island had an elevated risk, with an adjusted IRR of 1.30 compared with Southern ($p<0.001$).

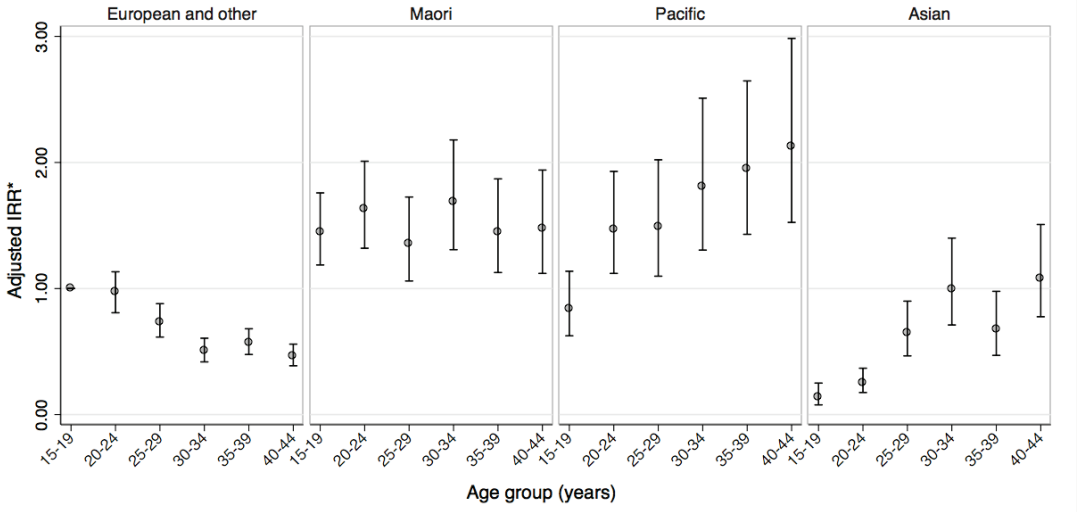
In all models, a 10% increase in deprivation (e.g. from decile 1 to decile 2) led to a statistically significant increase in the adjusted IRR of approximately 10%, such that comparing decile 10 with decile 1 would lead to a doubling of the risk of PID (refer to Appendix M for the full model results).

The relationship between the risk of PID, age group, and ethnic group was complex and varied for each PID category (refer to Figure 6.9).

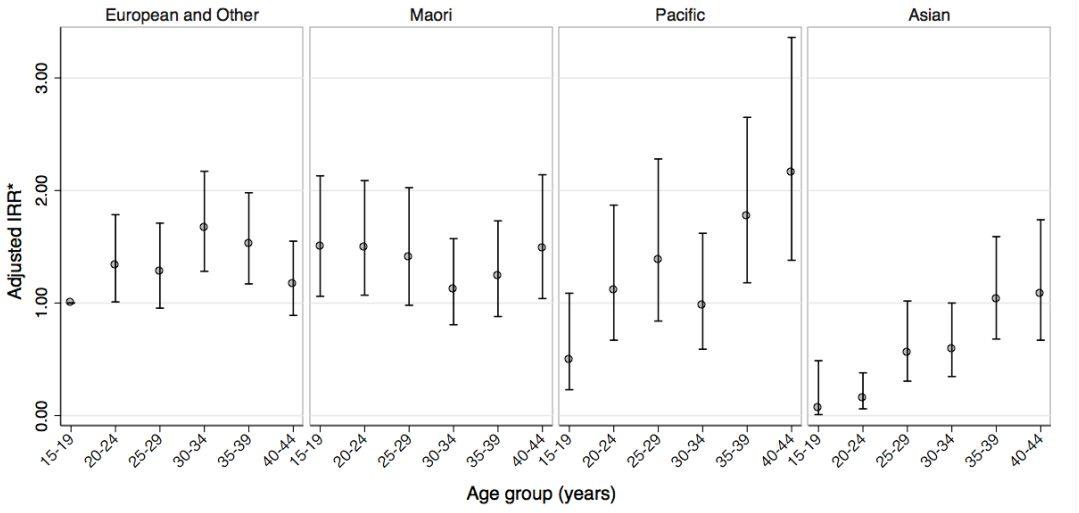
(A) All primary and secondary diagnoses



(B) Primary diagnoses only



(C) Confirmed diagnoses only



* *Adjusted for deprivation and geographical area.*

Figure 6.9: Adjusted* IRRs and 95% CIs for PID by age and ethnic group

For all primary and secondary diagnoses, Māori and Pacific women had the highest risk at ages 15–19 years (adjusted IRRs of 1.77 and 1.39 respectively) and 20–24 years (adjusted IRRs of 2.00 and 2.22 respectively) when compared with the reference group of European and Other ethnicity at age 15–19 years. From the age of 25 years the risk of PID diagnosis amongst Pacific women continues to climb to reach a peak adjusted IRR of 2.41 at age 40–44 years. For Māori, from the age of 25 years the IRR decreases to be similar to that of the European and Other ethnicity. The lowest risk of PID diagnosis is amongst young Asian women, at 15–19 years old the IRR is 0.15 compared with European and Other ethnicity, but this risk steeply increases with age reaching a similar risk to Māori, European and Other ethnicity at age 30–34 years. The risk by age for European and Other ethnicity remains relatively stable.

For primary diagnoses only, 15–19 year-old Māori women again have the highest risk (IRR of 1.45 when compared with European and Other ethnicity). However, the risk amongst Pacific women is similar to European and Other ethnicity. The risk amongst Pacific women climbs steeply with age to reach an adjusted IRR of 2.13 at age 40–44 years. For Māori women the risk remains elevated, but fluctuates by age with adjusted IRRs ranging from 1.34 to 1.69. Again, at young ages Asian women have the lowest risk with an adjusted IRR of 0.14 at age 15–19 years. However, this risk climbs with age, becoming higher than the risk for European and Other ethnicity for those aged 30–34 years. For European and Other ethnicity, the risk declines steadily with age; women at age 40–44 years had half the risk of those aged 15–19 years.

When considering only confirmed diagnoses of PID, the differences by ethnicity and age follow similar patterns to that of primary diagnoses for all ethnicities apart from European and Other. Māori women have an elevated but stable risk with age, with adjusted IRRs ranging from 1.13 to 1.50 compared with European and Other ethnicity at age 15–19 years. Pacific women have half the risk of European and Other ethnicity at age 15–19 years old, but this was not statistically significant, and the risk for Pacific women climbs with age to reach an IRR of 2.16 at age 40–44 years. Asian women again start with a very low risk at age 15–19 years (adjusted

IRR 0.07), but the risk climbs to meet that of European and Other ethnicity by age 40–44 years. For European and Other ethnicity the risk by age climbs to reach a peak of 1.67 at age 30–34 years.

6.4.4 Rates of ectopic pregnancy

Overall there were 19,796 cases of ectopic pregnancy during the time period 1988 to 2009, and 4,530 cases when looking in the most recent five-year period.

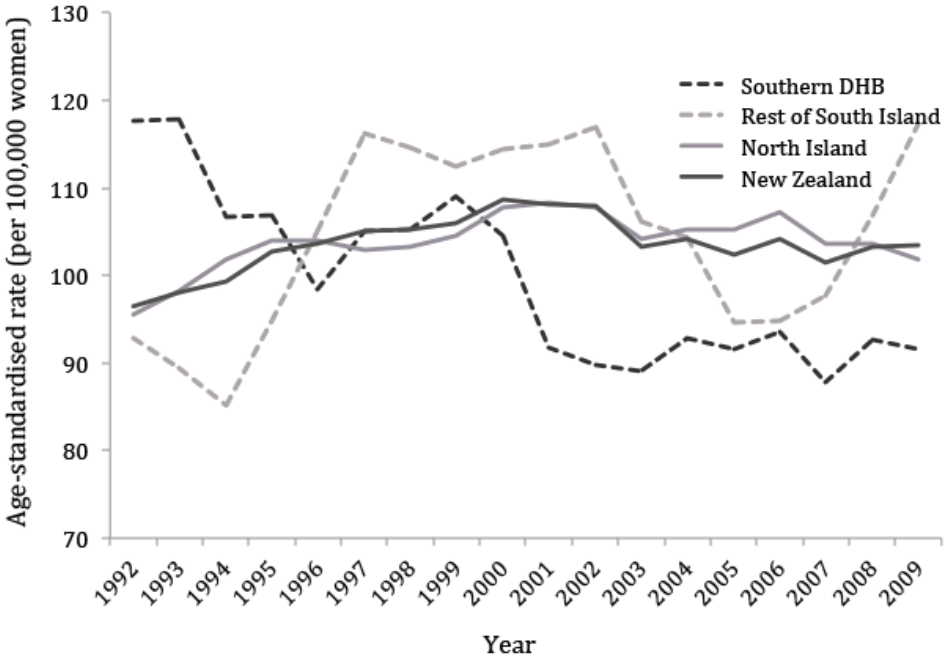
Time trends in ectopic pregnancy from 1988–2009

When analysing ectopic pregnancy age-standardised rates using the population of New Zealand women aged 15–44 years as a denominator, there was a slight increase in ectopic pregnancy age-standardised rates up until the early 2000s. Thereafter this increase plateaued, and in 2009 the overall age-standardised rate in New Zealand was 104.7 per 100,000 women (see Figure 6.10 overleaf). Yearly age-standardised rates of ectopic pregnancy were highly variable, but a clear pattern of decreasing age-standardised rates over time for Southern was seen in the 3-year moving average, with this decrease plateauing in the early 2000s. Since the early 2000s, the age-standardised rates have been lower in Southern than the rest of New Zealand. The trend in the North Island was almost identical to that for New Zealand overall, whereas the upper South Island has had very unstable rates with steep increases in the mid-1990s, steep decreases in the early 2000s and, more recently, steeply increasing age-standardised rates in the late 2000s.

Figure 6.12 shows the age-standardised rates of ectopic pregnancy by (a) population and (b) live births from 1988–2009. The rates per 1,000 live births reveal a similar trend in New Zealand to that of the population-based rates; increasing rates up until the early 2000s, thereafter plateauing. In 2009, the rate of ectopic pregnancy was 15 per 1,000 live births. Again, the North Island's pattern was almost identical to New Zealand overall, but in this case the rates for the whole South Island were highly variable and generally higher than the rates for the North Island. In Southern, the rates have generally been decreasing over time, whereas for the rest of the South Island there was a sharp increase in rates since

2006. In 2009, the age-standardised rates for Southern, the rest of the South Island, and the North Island were 17.5, 20.5 and 14.6 per 1,000 live births respectively.

(A) Ectopic pregnancy rates by population



(B) Ectopic pregnancy rates by live births

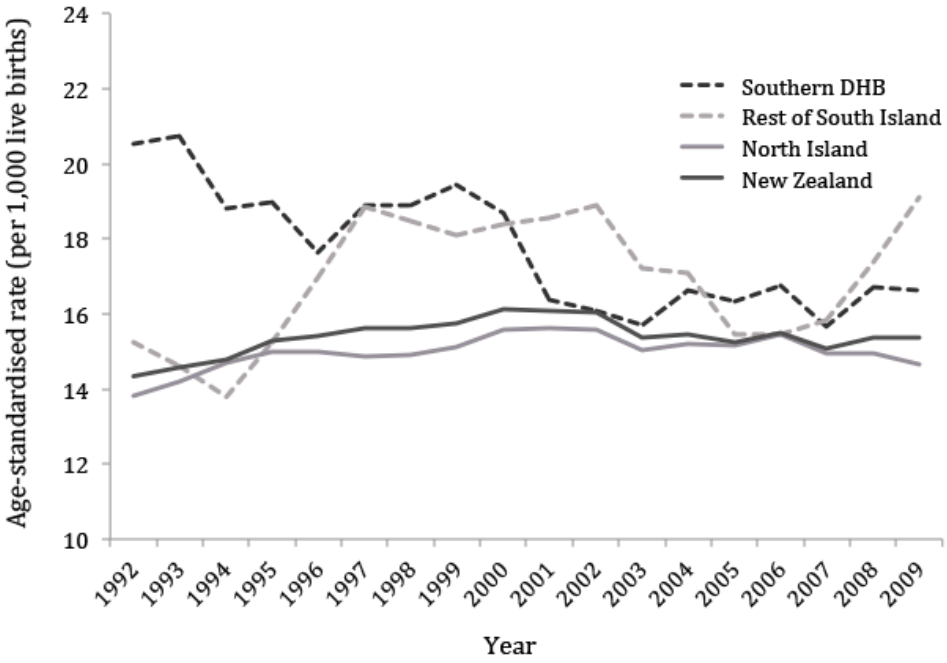
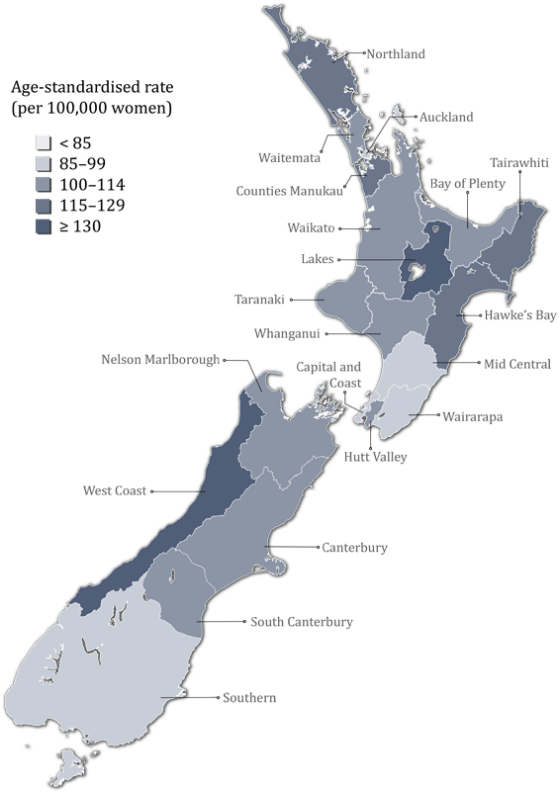


Figure 6.10: Age-standardised rates of publicly funded hospitalisations for ectopic pregnancy in women aged 15–44 years, 3-year moving average 1988–2009

Ectopic pregnancy by district health board from 2005–2009

Overall, the average annual age-standardised rate from 2005–2009 for ectopic pregnancy was 103.4 per 100,000 women and 15.3 per 1,000 live births. There was significant variation in age-standardised rates at the DHB level, with North Island DHBs generally having higher age-standardised rates for ectopic pregnancies by population compared with South Island DHBs, with generally lower age-standardised rates for ectopic pregnancies by live births (refer to Figure 6.11). Tables with specific age-standardised rates by DHB are in Appendix L on page 357.

(A) Ectopic pregnancy rates by population



(B) Ectopic pregnancy rates by live births

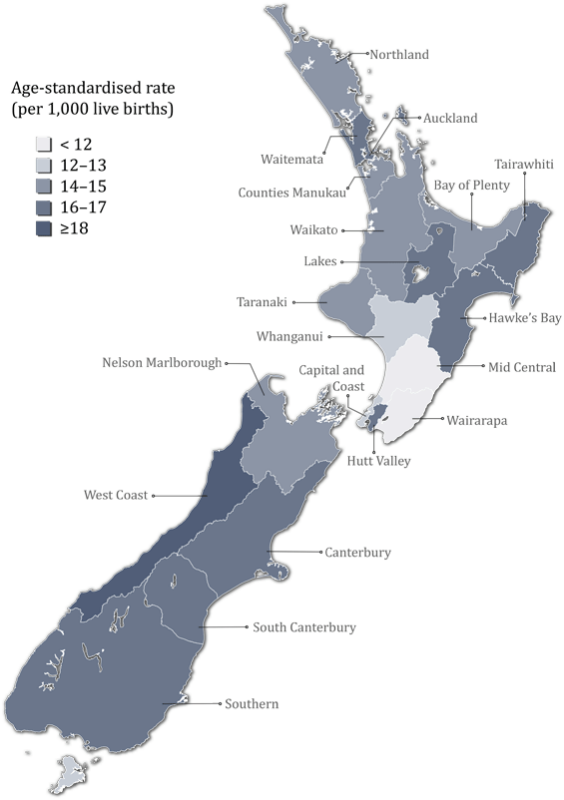


Figure 6.11: Age-standardised rates by DHB of publicly funded hospitalisations for ectopic pregnancy in women aged 15–44 years (average for 2005–2009)

Age, ethnicity and deprivation-specific rates of ectopic pregnancy from 2005–2009

Table 6.9 shows the age-specific rates for ectopic pregnancy during 2005–2009. By population, the highest rates of ectopic pregnancy were seen in women aged 25–34 years; a reflection of higher fertility in this age group. When examined by live births there was a trend of increasing rates by age group.

Table 6.9: Age-specific rates of publicly funded hospitalisations for ectopic pregnancy (average for 2005–2009)

Age group (years)	Rate per 100,000 women (95% CI)	Rate per 1,000 live births (95% CI)
15–19	37.6 (33.3–42.3)	12.8 (11.4–14.4)
20–24	119.7 (111.6–128.2)	15.8 (14.7–16.9)
25–29	171.1 (161.0–181.6)	15.2 (14.3–16.1)
30–34	170.4 (161.0–180.1)	13.9 (13.1–14.7)
35–39	110.8 (103.5–118.3)	16.9 (15.8–18.0)
40–44	30.6 (26.9–34.6)	24.2 (21.3–27.5)

Table 6.10 shows the age-standardised rates of ectopic pregnancy by ethnicity in women aged 15–44 years during 2005–2009.

Table 6.10: Age-standardised rates of publicly funded hospitalisations for ectopic pregnancy by ethnic group for in women aged 15–44 years (average for 2005–2009)

Ethnic group	Rate per 100,000 women (95% CI)	Rate per 1,000 live births (95% CI)
European and Other	96.5 (88.4–105.1)	15.9 (14.5–17.4)
Māori	148.4 (128.6–170.5)	16.3 (13.9–18.9)
Pacific	161.7 (129.7–199.2)	15.9 (12.7–19.7)
Asian	79.5 (62.8–99.2)	15.2 (11.5–19.8)

By population, age-standardised rates were highest in Māori and Pacific people. However, these groups also had the highest fertility rates in New Zealand. Examining the data by live births, age-standardised rates amongst European and Other ethnicity, Māori and Pacific people were very similar.

Table 6.11 shows the age-standardised rates of ectopic pregnancy by deprivation decile in women aged 15–44 years during 2005–2009. There were increasing age-standardised rates with increasing deprivation for both the population and births denominators. This indicates that whilst higher fertility in those with higher deprivation is responsible for some of the increase in the population-based age-standardised rates; there was also a higher risk of ectopic pregnancy per birth amongst the more deprived women.

Table 6.11: Age-standardised rates of publicly funded hospitalisations for ectopic pregnancy by relative deprivation in women aged 15–44 years (average for 2005–2009)

NZDep06 decile*	Rate per 100,000 women (95% CI)	Rate per 1,000 live births (95% CI)
1	64.5 (47.3–85.8)	12.4 (8.6–17.5)
2	78.9 (60.5–101.0)	13.2 (9.9–17.2)
3	74.3 (57.0–95.2)	14.5 (10.9–18.9)
4	72.6 (55.6–93.1)	13.1 (10.0–16.9)
5	95.7 (76.3–118.7)	14.6 (11.6–18.1)
6	86.1 (68.2–107.4)	14.7 (11.6–18.3)
7	115.7 (94.7–140.0)	17.5 (14.4–21.2)
8	131.1 (108.7–156.8)	17.4 (14.4–20.9)
9	145.8 (122.5–172.4)	19.4 (16.2–23.0)
10	146.3 (122.5–173.4)	17.5 (14.5–20.9)

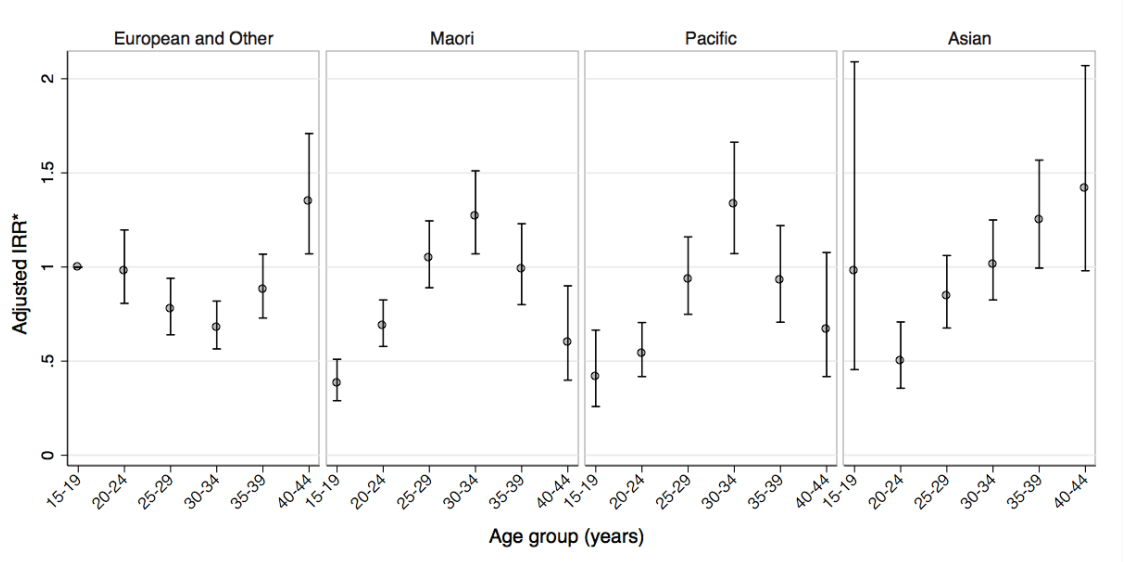
* *Where decile 1 is the population living in the 10% least deprived areas and decile 10 is the 10% most deprived.*

Risk of ectopic pregnancy from 2005–2009

A model was generated using live births as the exposure. There was a statistically significant interaction between age and ethnicity (p<0.001). Deprivation decile was added as a linear term only, as the quadratic term was not significant (p=0.544). All simultaneously adjusted independent variables were highly significant (all p<0.001). There was significant over-dispersion when checked using negative binomial regression (alpha statistic p=0.034). So, the final model was constructed using negative binomial regression rather than Poisson regression. Checking for zero-inflation using zero-inflated Poisson and negative binomial regression led to unstable models. Refer to Appendix M on page 364 for the table with the results of the final model.

Southern and the rest of the South Island had a similar risk for ectopic pregnancy diagnoses, however the adjusted IRR for the North Island was slightly lower (IRR 0.85, p<0.001). There was a statistically significant six per cent linear increase in the adjusted IRR for ectopic pregnancy per increase in deprivation decile.

The adjusted IRRs by age group did not display a clear pattern of increased risk of ectopic pregnancy by age (refer to Figure 6.12).



* *Adjusted for deprivation and geographical area.*

Figure 6.12: Adjusted IRRs with 95% CIs for ectopic pregnancy by age and ethnic group

Māori and Pacific women had almost identical patterns with decreased risk at age 15–19 years when compared with European and Other ethnicity (adjusted IRR 0.39 and 0.42 respectively), but this risk steeply increased and over took that of European and Other ethnicity at age 25–29 years, peaking at 30–34 years with adjusted IRRs of 1.27 and 1.34 for Māori and Pacific women respectively. The adjusted risk then steeply decreased. Asian women initially had the same risk as European and Other ethnicity, but sharply decreased to an adjusted IRR of 0.50 at age 20–24 years. Thereafter the risk for Asian women steadily increased with age, and was the only ethnicity to do so. For European and Other ethnicity, there was a moderate decline in the adjusted risk, with the adjusted IRR reaching 0.68 by 30–34 years, after this age the risk rose steeply.

6.5 Discussion

6.5.1 Patterns of infertility admissions

Hospital admissions for infertility in the publicly funded setting have decreased markedly over the time period 1988–2009 in all areas of New Zealand, although over time the South Island regions have maintained higher rates of infertility admissions than the North Island. Decreasing levels of infertility admissions could reflect three major trends: Inpatient infertility services converting to outpatient fertility services; surgery and other treatment being replaced by ART; and an increase in privately funded infertility services, especially with respect to accessing ART. There is no evidence internationally that the underlying prevalence of infertility is declining (Gurunath *et al.,* 2011) and fertility patterns in New Zealand would suggest that it is unlikely that infertility is declining here.

The age-standardised rates for infertility admissions from 2005–2009 revealed that these were more likely in Southern DHBs, in women in their thirties, and amongst women of European and Other ethnicity. These results could reflect a different balance of women who accessed privately funded care. However, given socio-economic patterns in New Zealand, accounting for privately funded services would most likely increase the difference between ethnicities. There was increasing publicly funded infertility hospital admissions with increasing

deprivation, although at the highest deprivations infertility admissions decline. For women in the least deprived categories, this could again reflect a different balance in access to privately funded services, rather than a lower prevalence of infertility in the population.

The effect of area and deprivation remained similar to the patterns shown by the age-standardised rates when modelled. However, the differences in access by ethnicity became greater, with European and Other ethnicity aged 30–39 years having much higher adjusted IRRs for infertility admissions. The model possibly exaggerates differences between ethnicities, as it does not account for differing levels of fertility by ethnicity and age, with European women having children later and, therefore, more likely to experience age-related infertility. However, with such large differences by ethnicity in the IRRs, it seems very likely that Māori and Pacific women have far less access to infertility services than European and Other ethnicity. It is unlikely that this difference could be explained by differing access to privately funded infertility services, or by a much lower underlying prevalence of infertility in Māori and Pacific women. This difference would then indicate a concerning lack of provision of infertility services for these women and their partners. Whether this is because the services are not available, or these women do not qualify for publicly funded services, or the service is not culturally appropriate, or another reason, is not discernable from these data.

6.5.2 Patterns of pelvic inflammatory disease admissions

The increasing levels of combined primary and secondary diagnoses of PID from 1988–2009 conflict with the published data from New Zealand (Morgan *et al*., 2011). The previously published data were limited to just primary diagnoses, and primary diagnoses of PID have decreased over time. This could be accounted for by ascertainment biases. It is probable that a primary diagnosis of PID is more likely to reflect an acute and more recent case of PID, whilst there is probably a higher proportion of previous undetected (old) PID amongst secondary cases. However, as these data were de-duplicated and include first PID diagnosis only, this bias has been reduced. Therefore, excess detection of old PID in secondary diagnoses is

unlikely to completely account for the divergent trends between all diagnoses of PID and primary diagnoses of PID. The divergence in primary PID and all primary and secondary PID diagnoses would support the theory that PID is becoming less acute as ever greater proportions of PID are being caused by *C. trachomatis* compared with *N. gonorrhoea* (Rolfs *et al., 1992,* Kamwendo *et al., 1996*), and, therefore, a higher proportion of cases are being picked up as secondary diagnoses. This would also likely lead to a greater proportion of cases being seen in the community, and therefore the increasing rate in all diagnoses of PID may be underestimated.

Rates of primary PID diagnoses in New Zealand reported previously by Morgan *et al*. (2011) and Bender *et al.* (2011) for 2008 were almost double the rates seen in this analysis. The data previously reported for New Zealand was estimated from three North Island regions, which had relatively high rates of PID when compared with South Island regions. Also, data presented in this analysis were de-duplicated and all repeat admissions for PID were removed. Rates for primary PID at around 100 per 100,000 women remain high compared with other countries. However, due to the amount of uncertainty regarding the accuracy of PID diagnoses, and that the proportion of PID that gets diagnosed in hospitals is likely to vary substantially between countries, such comparisons are probably not valid. It seems unlikely that PID in the population is decreasing over time as suggested by the age-standardised rates for primary diagnoses of PID, especially given the substantial increases in all primary and secondary diagnoses of PID. If a similar pattern is occurring regarding the primary reason for admission to hospitals in other countries, then any analyses over time may have under-estimated the levels of PID seen in hospitals.

The risk of PID varied by DHB, ethnicity, age and deprivation. Generally, the South Island and Southern had lower rates of PID. For primary diagnoses of PID, those aged less than 25 years had the highest risk of PID, most probably due to the higher rates of STIs seen in this age group. For all primary and secondary diagnoses of PID the highest risk was for women aged 20–39 years. This result may reflect either excess detection of old PID, or other causative agents for PID, or reflect the risk of PID in relation to puerperal infection. Māori and Pacific women

had substantially elevated rates of PID; the results for Māori women confirmed those of the earlier analysis presented in Reynolds and Smith (2012). Those with higher levels of deprivation had higher levels of PID. Whilst there has been little published work on a hospitalisation data taking into account an SES measure, given the relationship between SES and STIs, this result was expected.

After simultaneously controlling for all of the demographic measures in a model there remained statistically significant differences for all of the demographic measures. Southern DHB had half the risk of PID compared with the rest of the South Island and the North Island. When examining ethnicity effect modification by age was apparent. For all ethnicities except European and Other ethnicity, the risk of primary diagnoses of PID actually increases in risk with age, but as the European population is much larger, overall primary diagnoses decreases with age. The age trends amongst European and Other ethnicity are comparable to data from other studies that show PID rates are highest amongst young women. This result is probably due to the relatively high incidence of STIs amongst young women. The divergence in trend for Māori, Pacific and Asian women may reflect differing access to healthcare with later diagnosis, or a differing underlying incidence by age. IRRs amongst Māori and Pacific women were higher than all other ethnicities for all age groups 20 years and older. When considering all primary and secondary diagnoses of PID there was a similar pattern for Pacific women, IRRs increased with age and were higher than all other ethnic groups. For Māori women, IRRs decreased with age from 25 years, and for European women the effect of age was not substantial. Overall, apart from confirmed diagnoses, Māori and Pacific women have the highest risks, and Asian women the lowest. The reasons for different age specific patterns by ethnicity in New Zealand need further examination. Whether the cause of these differences is due to different underlying rates in the population or differences in health care access, there remain important and substantial disparities in the risk of hospital diagnosed PID between ethnic groups in New Zealand.

6.5.3 Patterns of ectopic pregnancy admissions

The levels and patterns of ectopic pregnancy diagnoses are very different when using a population-based denominator versus a fertility-based denominator (live births). These differences are a reflection of the highly varied fertility patterns in the different population strata in New Zealand. There is higher level of fertility in the North Island, and higher levels of fertility amongst Māori and Pacific women. Therefore, as these groups have more exposure to the risk of an ectopic pregnancy, their rates of ectopic pregnancy are highly elevated in the population. Using the denominator of live births adjusts for the confounding effect of fertility rates, but some fertility is not accounted for (miscarriages, terminations and still births), therefore, there will be some residual confounding.

Overall rates of ectopic pregnancy of 104.7 per 100,000 women and 15.6 per 1,000 live births in 2009 were slightly lower than that reported by Morgan *et al.* (2011). The majority of this discrepancy is most likely a result of the current analysis including data from all of New Zealand and these data did not include repeat admissions. Unlike many other countries, the rate of ectopic pregnancies in New Zealand has not declined over the time period 1988–2009. In contrast, increasing rates were seen into the 2000s, with the rate more recently remaining stable. If there is a trend towards more ectopic pregnancies being diagnosed early and treated as outpatients in recent years, it follow that the incidence of ectopic pregnancy is probably increasing. However, without data from outpatients it is not possible to estimate the magnitude of this effect.

Comparison of age-standardised rates using live births as the denominator showed minimal differences by age group, apart from the 40–44 year-old group who had a substantially elevated rate. Differences by ethnicity were also not apparent. It is possible that the differences in the Māori and non-Māori rates previously reported by Reynolds and Smith (2012) actually reflects higher fertility in Māori as a population-based denominator was used. Differences by areas in the rates were apparent, with the South Island regions generally having higher rates of ectopic pregnancy. PID is a major risk factor for ectopic pregnancy. So, given the

substantially elevated risk of hospital diagnosed PID for Māori and Pacific women and the higher rates in the North Island, it does not seem plausible that the South Island has higher rates of ectopic pregnancy, and the rates are similar by ethnicity. Ectopic pregnancy risk is also increased by smoking, however, the confounding effect of smoking would more likely lead to elevated rates amongst Māori and Pacific women as they have a higher prevalence of smoking than European women. However, there are many remaining confounding effects, including residual confounding from the fertility denominator, which may explain this. It may also be that overall North Island DHBs have a higher proportion of cases managed as outpatients, which would impact on both the geographical trends and trends by ethnicity.

Modelling the age and ethnicity specific patterns whilst controlling for deprivation and area revealed only minimal confounding by area, although it would be unlikely that the patterns of healthcare provision in New Zealand can be explained by dividing New Zealand into three areas. However, this model did reveal differing age specific risks by ethnicity. For Māori and Pacific women, this risk increased with age up to age 30–34 years, and then decreased. However, for European and Other ethnicity the risk was exactly the opposite: decreasing somewhat up to the age 30–34 years, and then steeply increasing. For women of all ethnicities, it is unlikely that the risk of ectopic pregnancy decreases with increasing age. The most likely explanation for the patterns seen in these data are that for women experiencing ectopic pregnancies in the time period 2005–2009, the results were confounded by differing prevalence by age of unmeasured risk factors (e.g. smoking).

6.5.4 Limitations

Ectopic pregnancy is an acute condition and not very likely to be misdiagnosed or not diagnosed at all. The evidence in New Zealand is that probably the majority of cases are still treated as hospital inpatients (although probably with an increasing proportion being treated as outpatients over time). Therefore, it is likely that

ectopic pregnancy is a more robust indicator of tubal factor infertility risk than PID or infertility.

Certain limitations must also be considered when interpreting the PID data. PID diagnosis is known to be subjective and possibly inaccurate. It is also likely that, especially for asymptomatic PID, the majority of cases remain undiagnosed, and the remaining cases are more likely to be treated in the community and not as hospital inpatients. The underlying patterns of health care access by various groups (e.g. by ethnicity and/or deprivation decile) would influence rates of diagnosis. So, higher levels of hospitalised care could reflect higher levels of disease, or less access to primary health care resulting in worse disease progression and higher use of hospital services. Given this, PID hospital inpatient diagnoses are most likely not a robust measure of PID disease rates in the population.

Similar limitations apply when interpreting infertility diagnoses, although there is not likely to be the same level of inaccuracy in the diagnosis. Also, there is not a good denominator; not all women are at risk of infertility. Furthermore, of those that choose to use infertility services, about half opt for privately funded treatment (Peek, 2015), and privately funded hospital admissions are not collected in the National Minimum Dataset.

6.5.5 Conclusion

Overall, this analysis gave an overview of trends in hospitalisation for infertility, PID and ectopic pregnancy in New Zealand and provided comparative data for the Southern DHB contrasted to other areas and New Zealand in general. This analysis is relevant when considering the generalisability and wider implications of the infertility patterns in Otago and Southland being investigated in this thesis.

Rates for all of the investigated outcomes varied between Southern DHB and the rest of New Zealand, with Southern having lower PID, similar or higher ectopic pregnancy rates, and higher rates of infertility hospitals admissions when compared with the rest of New Zealand. These results remained similar after

simultaneously adjusting for the confounding effects of age, ethnicity and deprivation. How this information influences the generalisability of infertility data from Southern DHB in Chapters Three and Four is difficult to interpret, it is plausible given the PID data, that Southern DHB may have lower rates of tubal factor infertility than the North Island. However, PID is also one of the contributing factors in ectopic pregnancy, yet ectopic pregnancy was no different by region in New Zealand. Therefore, it cannot be inferred from these data that if various population subgroups have higher levels of hospital-diagnosed PID they will have higher levels of infertility, especially as tubal factor infertility is not likely to be the main cause of infertility in New Zealand.

The lack of similarity between PID and ectopic pregnancy patterns was also evident in the ethnicity patterns. Specifically, PID rates were highest amongst Māori and Pacific women, yet ectopic pregnancy rates were only elevated in specific age groups. The data also indicated a possible lack of infertility service provision for Māori and Pacific women, which warrants further investigation.

Overall, in view of the changes in the provision of care for the conditions examined, particularly infertility, and other difficulties in the interpretation of the findings, hospitalisation data are not likely to provide robust data from which recent time trends, or geographic and demographic patterns of disease, can be inferred with reasonable certainty. Due to the substantial uncertainties regarding case ascertainment, and also the validity of diagnosis for PID, analyses of hospitalisation data are not currently a feasible method of monitoring infertility or indicators of tubal infertility risk. Other potential administration datasets, such as GP visits, privately funded specialist fertility visits, or outpatient diagnoses are not available nationally in New Zealand, and without such data there is very limited utility in analysing routine datasets to monitor infertility, PID or ectopic pregnancy.

CHAPTER SEVEN:

SUMMARY AND DISCUSSION OF RESEARCH

Chapter Seven summarises and discusses the results of the three studies, compares the findings with the international and national literature, examines the relative strengths and limitations of the studies in this thesis, concludes on the importance of its findings, health care provision and policy implications, and considers future directions for research.

As discussed in the introduction to this thesis, a trend towards delayed childbearing and smaller family sizes has been a commonly observed phenomenon in middle to high-income countries such as New Zealand. In recent years this increase in the median age of first birth and decrease in the TFR has stabilised or even slightly reversed in many OECD countries. However, for individuals, concerns regarding the effect of these trends on infertility and involuntary childlessness remain. It is well recognised that women's fecundity declines from the age of 30 years, and more markedly in the mid to late-thirties. With the median age of first birth for women having stabilised at 30 years in New Zealand, it is possible that age-related infertility will have become common in this social environment, where delayed fertility is the norm. Whilst there have been many studies on infertility in other high-income countries, there has been very little population-based research in New Zealand. Therefore, results from the studies in this thesis provide a unique insight into infertility in New Zealand.

7.1 Infertility in Otago and Southland

The population and clinic-based studies of infertility in Otago and Southland successfully fulfilled the first two aims of this thesis (refer to Section 2.11 on page 67 for the aims). Together these studies provide a consistent representation of infertility in Otago and Southland, with the results revealing common findings for comparable measures.

7.1.1 The prevalence and predictors of infertility

Infertility was common amongst women in Otago and Southland who had ever tried to conceive or had a pregnancy; one in four (25.3%, 95% CI 22.6–28.1%) had tried for at least 12 months or had sought medical help to conceive. This measure, and that of having tried to conceive for 12 months or more (21.7%, 95% CI 19.1–24.4%), was slightly higher than studies in other high-income countries (as shown in the literature review in Section 2.6 from page 30). Whilst these measures varied markedly by country, on average, around 19% of women had ever tried for 12 months or more to conceive (refer to Figure 2.2 on page 32 to view the forest plot for these study estimates). However, recent data published from a cohort born in Dunedin in 1972/3, which had questions on infertility when participants were aged 32 and 38 (van Roode *et al.*, 2015), had very similar prevalence estimates to this survey (26.0% for trying for at least 12 months or seeking medical help to conceive).

After controlling for education and relationship status, the survey data showed that an increased risk of infertility was associated with being underweight (RR 2.61, 95% CI 1.43–4.79) or in obese classes II or III (RR 1.78,95% CI 1.19–2.65 and RR 2.01, 95% CI 1.19–3.37) compared with normal BMI. This result corresponds well with that of Hassan and Killick (2004), who found that being underweight was associated with a quadrupling and being in obese class II or III with a doubling of the time to pregnancy.

The risk of infertility was also modestly increased amongst women who had a university level qualification (RR 1.19, 95% CI 1.04–1.35) compared with those without such a qualification, as found previously in Finland and New Zealand (Terava *et al.*, 2008, van Roode *et al.*, 2015).

The risk of infertility was reduced (RR 0.50, 95% CI 0.28–0.90) amongst women who were single or in a same-sex relationship compared with women in a heterosexual relationship at the time of the survey; this was despite limiting this to women having tried to conceive or having had a pregnancy. However, it is possible that women who were not in a heterosexual relationship may have had less

exposure to pregnancy risk and, therefore, infertility in the past. There was no statistically significant association between being infertile and deprivation (based on residential area) or ethnicity.

7.1.2 Infertility service use

The majority of infertile women in the survey accessed primary and/or specialist care for infertility. Two-thirds sought primary health care and just under half help from a specialist. It is difficult to compare these figures to those from other middle to high-income countries due to the varying and often poor definition of service use utilised. It is also likely that the level of specialist service use has reduced in recent years in New Zealand, as up until 2005 all specialist infertility referrals were accepted, irrespective of BMI or smoking status, which is no longer the case (Gillett, 2015).

Infertile survey participants' service use and outcomes were examined in detail for their first episode of infertility (refer to Figure 3.3 on page 104). This analysis showed over 90% of women resolved their first episode of infertility and/or sought the appropriate medical care. This suggests in the Otago and Southland region that specialist, and especially, non-specialist infertility care was both accessible and acceptable to the vast majority of women who have fertility concerns. However, this analysis also revealed that almost 10% of these women had not had a live birth after this first episode of infertility and, therefore, may have benefited (by receiving advice and/or treatment to resolve their infertility) if they had accessed infertility care.

Educational level and household income were associated with service seeking amongst infertile survey participants. Those who had a university level qualification were slightly more likely to seek non-specialist medical services than those without a university level qualification (RR 1.10, 95% CI 1.01–1.21). Those in the medium household income bracket were less likely to access specialist care than those in the high-income bracket (RR 0.67, 95% CI 0.49–0.90). Similar associations have been found in other population-based studies in Finland and the USA (Terava *et al.*, 2008, Chandra and Stephen, 2010). In England social class was

also found to be important (Gunnell and Ewings, 1994), but the area-based measure of deprivation available in this thesis' population-based survey was not associated with service seeking. Parity has also been found to be an important predictor of accessing services (Schmidt *et al.*, 1995, Terava *et al.*, 2008, Chandra and Stephen, 2010), but this was not the case for women in this thesis' survey.

In New Zealand, age, BMI and smoking are all factors that impact on the likelihood of receiving publicly funded infertility treatment, as they influence the probability of a positive treatment outcome (Gillett *et al.*, 2012). However, these factors were not associated with seeking specialist infertility care. This suggests non-specialist providers were not influenced by the likelihood of receiving funding and/or treatment success when referring women to specialist providers. This may reflect that referral rules prior to 2012 were relatively relaxed, as most infertility clinics no longer accept a referral for a woman who is a smoker or has a BMI outside the accepted range (Gillett, 2015). Prior to 2012 all referred women, regardless of their suitability for treatment, were scored using the CPAC tool, thereby determining whether they would qualify for public funding. However, women could only then access publicly funded treatment if they met the BMI and smoking criteria. Therefore, women who did not meet these criteria were placed on active review until they met the criteria, had a spontaneous birth or withdrew from care.

Whilst almost half of infertile women participating in the survey reported seeing a specialist for infertility, analyses of the clinic-based data revealed that withdrawal from infertility care was not uncommon, with one in eight patients doing so. After adjusting for multiple risk factors in a regression model, it was found that the risk of withdrawal was elevated for patients in the highest deprivation group, who were almost 70% more likely to withdraw than those in the lowest deprivation group (RR 1.67, 95% CI 1.18–2.34). There was also an elevated risk of withdrawal amongst Māori women/couples compared with European (RR 1.55, 95% CI 1.03–2.32). Amongst smokers the relative risk was 1.44 (95% CI 1.09–1.92) times that of non-smokers and amongst those with a BMI in the obese II and III classes the relative risk was 1.83 (95% CI 1.17–2.87) and 2.04 (95% CI 1.32–3.18) respectively, compared with a normal BMI. An Australian population-based study

found similar associations for BMI and smoking with *service access*, but no information on withdrawal from services was provided (Herbert *et al.*, 2009).

It is possible that the increased risk of withdrawal for women with higher BMIs and women who were smokers was related to the restrictions on public funding and treatment for infertility for women in these risk groups, although qualifying for public funding was not directly associated with withdrawal for clinic patients. However, the elevated risk of withdrawal for more deprived women and Māori women is of concern and should be further investigated.

7.1.3 Diagnosed cause(s) of infertility

The most common causes of infertility amongst survey participants who had consulted a specialist were male factors (33.3%), ovulation disorders (24.6%) and unknown cause (23.7%). This was very similar to self-reported causes of infertility in Scotland (Bhattacharya *et al.*, 2009), where ovulation disorders, sperm quality problems and unexplained causes were also the most common. This was consistent with much of the reviewed research, with just two studies reporting higher proportions of tubal disorders (an older study from Australia and a slightly more recent study in the USA) (Weiss *et al.*, 1992, Stephen and Chandra, 2000).

The majority of patients in the clinic-based study received a diagnosis and, similar to the survey participants, the most common diagnoses amongst patients were semen problems in their male partners (36.5%) and their own ovulation disorders (25.1%), with multiple factors present in just over a quarter of patients. Female factor infertility was diagnosed in 55.4%, male factor in 39.3% and combined factor in 14.6% of patients.

7.1.4 Treatment uptake

Over a third of infertile survey participants reported receiving infertility treatment. Of the women who saw a specialist, three-quarters reported receiving treatment, the most common forms of treatment being drugs (50.5%) and IVF (39.3%). In other population-based studies, the proportion of infertile women who self-reported receiving treatment varied considerably, from 9–33% (refer to Table

2.1 on pages 37–41 for an overview of these studies). However, as was the case for service use, comparisons with other studies are difficult as often treatment was not well defined or the definition varied, as did the timeframes and definitions for their infertility diagnosis (unprotected intercourse for 12 or 24 months and trying to conceive for 12 or 24 months).

Almost two-thirds of clinic patients received some form of treatment (IVF, surgery, IUI/DI or OI). While this treatment estimate is lower than that reported by the survey participants, there was no difference between the two studies regarding the prevalence of IVF and IUI/DI procedures. Survey participants reported significantly higher uptake of surgical procedures and drugs and it is possible that they included non-treatment surgical procedures (such as investigation by laparoscopy) and prescriptions from secondary care providers and/or GPs when answering treatment questions. If so, this could explain the differences in treatment uptake between the two studies.

Unlike the survey finding for service access, the likelihood of treatment in the clinic-based study was associated with parity; those with children were 17% less likely than those without (RR 0.83, 95% CI 0.75–0.91). Those in the age group 40–49 years were 27% less likely to receive treatment than those aged 30–34 years (RR 0.73, 95% CI 0.59–0.89), those who smoked 14% less likely than those who did not (RR 0.86, 95% CI 0.77–0.96), and those with a BMI in obese class II or III 25% (RR 0.75, 95% CI 0.58–0.97) and 58% (RR 0.42, 95% CI 0.27–0.67) respectively) less likely than those with a normal BMI. It is possible that the reduced likelihood of treatment amongst older women, smokers and those with non-optimal BMIs was related to both funding access and the reduced probability that the treatment would be successful. Although no relationship was detected between treatment and qualifying for public funding after statistical adjustment for other factors associated with receiving treatment, it may be that qualifying for funding was on the causal pathway between these factors and treatment. Patients with combined diagnostic severity scores of moderate and above were twice as likely to receive treatment when compared with those who had a minimal score,

which is to be expected given the CPAC assessment procedure (refer Section 4.1 on pages 155–156 for an introduction to CPAC).

7.1.5 Resolution of infertility

Three-quarters of infertile women who participated in the survey resolved their first episode of infertility with a live birth. Women were less likely to do so if they were aged 35 years or more at onset of first infertility (RR 0.71, 95% CI 0.53–0.96) or if they were in the more deprived groups (RR 0.89, 95% CI 0.80–1.00). Service access did not explain the lower rate of resolution amongst highly deprived women, as deprivation was not associated with accessing a non-specialist or a specialist medical provider. However, clinic data did show that more highly deprived women who attended the specialist service were more likely to withdraw than less deprived women.

The proportion of women who resolved their infertility with a live birth was high, with three-quarters of women having a live birth after their first episode of infertility. Yet, a relatively high proportion of women over the age of 40 years were involuntarily childless (6.7%), or had fewer children than they desired (27.4%). Involuntary childlessness and having fewer children than desired were both strongly associated with having experienced infertility in the survey. This suggests that lack of opportunity was probably not the main cause of involuntary childlessness and having fewer children than desired. The estimate of involuntary childlessness was higher than the 4% figure seen in the reviewed population-based surveys (refer to Table 2.1 on pages 37–41 for an overview of these studies).

Amongst women who attended the OFS, 54.2% resolved their infertility at a rate of 33.2 (95% CI 30.9–35.6) live births per 100 person years of observation. These estimates include the patients that withdrew from care and, therefore, if they had a future live birth it was not recorded, thus providing a conservative estimate of resolution. Resolution was lower for the clinic patients than for women participating in the survey, but survey participants who accessed specialist care also had a reduced level of resolution (54.7%), virtually identical to that found in

the clinic sample; this may be because women who attend specialist care have more serious infertility problems.

Amongst patients in the clinic study, levels of resolution were reduced amongst those in same-sex relationships or single compared with those in heterosexual relationships (RR 0.49, 95% CI 0.33–0.74), those aged 35–39 years (RR 0.69, 95% CI 0.61–0.78) and 40 years or more (RR 0.34, 95% CI 0.25–0.47) compared with age 30–34 years and amongst patients of high deprivation compared with low deprivation (RR 0.75, 95% CI 0.64–0.87). A combined diagnostic severity score was used to assess the number and severity of all diagnoses simultaneously in one measure. An increased combined diagnostic severity score was associated with a reduced level of resolution; the likelihood was halved for those with 'severe' compared with 'minimal' severity (RR 0.57, 95% CI 0.49–0.66). There was a considerable reduction in the likelihood of resolution for patients who spent four or more years in care, compared with those patients who spent six months or less (RR 0.33, 95% CI 0.24–0.43). Increasing level of treatment predominance was associated with increasing resolution of infertility, such that IVF doubled the probability compared with no treatment (RR 2.05, 95% CI 1.77–2.37).

Data from previous research suggested that over 50% of infertile women either spontaneously conceive or conceive with treatment (refer to Section 2.7.1, pages 50–52, for further details of the reviewed studies). This was very similar to the survey and clinic data for women who attended specialist care, but lower than the finding for all women on their first infertility experience. However, these studies may have measured resolution after the most recent infertility episode, which would be expected to be lower than that for the first episode, as some women have multiple episodes of infertility. Success rates in these studies appeared to be either similar or slightly lower for women who received treatment. This again probably reflects a more severe form of infertility in women who receive treatment, rather than reflecting on the benefit of having treatment, although this level of detail was not given in any of the studies and models controlling for diagnostic severity and length on infertility were not evident.

7.1.6 Fertility knowledge and behaviours

Survey participants were asked five infertility knowledge questions, 39.0% of women answered one of these questions correctly and 29.1% answered two questions correctly, less than 1% answered all questions correctly. Knowledge levels were not associated with being infertile or with age. Responses to natural fertility questions were optimistic, with over a third of respondents believing that an average woman was fertile for six days or more during one menstrual cycle. Over a third of women reported that fertility declines from age 35 years and almost a quarter from 40 years of age. These findings of poor knowledge levels and over optimistic responses were in common with the reviewed studies of infertility knowledge (refer to Section 2.8.1, pages 70–72, for further details of these studies).

There were no previous studies identified that provided information on women's ovulation monitoring behaviours in the general population. Survey participants were questioned on their knowledge of the fertile window and on whether they had attempted to monitor their own ovulation. A third of participants reported monitoring their ovulation, most commonly for the purpose of conceiving. The most common method was using a calendar to chart the menstrual cycle (and thereby deduce approximate ovulation dates), followed by basal temperature monitoring (which involves identifying the temperature spike that occurs at the time of ovulation). According to Sievert and Dubois (2005), these methods have varying degrees of accuracy, but it is unlikely any are accurate more than half the time. A recently published study by Hampton *et al*. (2013) amongst a small group of women attending specialist infertility services in Australia found that timing of intercourse for the perceived fertile window was common. However, very few of these women could accurately identify when they ovulated. The authors concluded that poor fertility awareness might in fact have contributed to their infertility.

It is not known whether women participating in the population-based survey in this thesis correctly used ovulation monitoring, interpreted the results accurately and applied this knowledge in a useful way. The results did reveal poor knowledge

of the infertility window (and overall poor knowledge) and that significant numbers of women learned about ovulation monitoring techniques via the internet and/or friends/family members. Therefore, it is possible that many of these women may not have been applying these techniques in a way that was beneficial for conceiving.

7.2 Using hospitalisation data to measure infertility and associated conditions in New Zealand

The assessment of infertility using routinely collected data such as hospital discharges is challenging; trends in publicly funded infertility hospitalisations are likely to be strongly influenced by health systems, funding policies, and changing technologies. However, in the absence of any national information on the infertility it was hoped that a review of hospital admissions with infertility discharge diagnoses could provide a feasible method for exploring trends in New Zealand. Furthermore, exploring these trends may have provided evidence as to whether the population and clinic-based research in Otago and Southland could be generalised to other regions of New Zealand. Given there is a relationship between PID, ectopic pregnancy and tubal factor infertility, and the likely difficulties associated with assessing infertility hospitalisations, PID and ectopic pregnancy hospital admissions were also analysed.

Whilst assessment of infertility using routine datasets has rarely been undertaken previously, rates of PID and ectopic pregnancy have been investigated in some European countries and states of the USA using hospitalisation datasets (refer to Section 6.1.4, pages 213–216 for details of the reviewed studies). While overall rates have been decreasing since the 1980s, there is evidence of very recent increases. New Zealand appears to have some of the highest rates of PID and ectopic pregnancy in high-income countries (Bender *et al.*, 2011). Furthermore, the issues of PID in relation to ectopic pregnancy and tubal factor infertility are particularly important in addressing health disparities within New Zealand. Published evidence strongly suggests that Māori women have a disproportionate burden of diagnosed *C. trachomatis* infection (which can lead to PID and ectopic

pregnancy), PID, ectopic pregnancy and possibly tubal factor infertility (The Institute of Environmental Science and Research Ltd., 2012, Reynolds and Smith (2012).

It appears that rates in recent years for all of the investigated outcomes vary between Southern DHB and the rest of New Zealand, with Southern DHB having higher rates of infertility hospital admissions, lower rates of PID and similar or higher ectopic pregnancy rates when compared with the rest of New Zealand. These results remained similar after simultaneously adjusting for the potentially confounding effects of age, ethnicity and deprivation. It can be inferred, given the PID data, that Southern DHB may have lower rates of tubal factor infertility than the North Island, suggesting that the clinic-based study and the survey under-estimate the burden of tubal factor infertility in New Zealand. However, PID is also one of the contributing factors in ectopic pregnancy, yet ectopic pregnancy was no different by region in New Zealand. Therefore, it cannot be inferred from these data that if various subgroups have higher levels of hospital diagnosed PID they will have overall higher levels of infertility, especially as tubal factor infertility is still not likely to be the main cause of infertility in New Zealand.

The lack of similarity between PID and ectopic pregnancy patterns was also evident in the ethnicity patterns. Specifically, PID rates were highest amongst Māori and Pacific women, yet ectopic pregnancy rates were only elevated in specific age groups.

The data also indicated that the high and apparently equitable service access seen in Otago and Southland may not be generalisable to the rest of New Zealand, as other regions appeared to have lower publicly funded hospital discharges for infertility. There also appeared to be a possible lack of infertility service provision for Māori and Pacific women, which warrants further investigation.

It is highly likely that many PID cases remain undiagnosed or were not treated as hospital inpatients and an increasing number of infertility and ectopic pregnancy cases were also not being treated as inpatients (refer to Section 6.1.3, pages 211–213, for a more detailed discussion on the limitation of using hospital discharge

data for these conditions). Therefore, the reliability and robustness of these data are very questionable, especially given the disconnect between PID and ectopic pregnancy trends.

Thus, firm conclusions about these trends and the generalisability of the studies from Otago and Southland cannot be made.

7.3 Strengths and limitations of research

7.3.1 Strengths of the population-based survey

This thesis' population-based survey had a well-characterised sampling frame with very good population coverage in the age group included in this study. Basic demographic information was available for both the survey responders and non-responders, including the incorporation of an SES measure (the deprivation score). The use of a computer-based questionnaire minimised data coding and entry errors, standardised the presentation of the questionnaire (compared with using interviewers) and may have encouraged more complete disclosure of sensitive data; it also allowed for a comprehensive set of fertility questions to be presented. This comprehensive assessment uniquely allowed the construction of the complete pathway from the first experience of trying to conceive for 12 months or more (being infertile) through to various forms of service seeking. Resolution of infertility at various stages of this pathway could also be examined. Findings for the cross-sectional study were very well supported by similar findings from the less subjective clinic-study data (where there were analogous measures). Findings on the overall prevalence of infertility were supported by a separate cohort study in the region, which had very minimal loss to follow up.

7.3.2 Strengths of the clinic-based study

This thesis' clinic-based study examined a relatively large cohort of patients, with all patients followed until conclusion of their treatment programme or for at least five years. Data from these patients provided a unique opportunity to examine

predictors of programme withdrawal, receiving treatment and resolving infertility. Diagnoses were not self-reported like the majority of population-based studies, but provided by objective clinical assessment by just two clinicians, minimising variations. Diagnoses and their impact on treatment uptake and resolution of infertility can be difficult to assess, as frequently patients have more than one diagnosis that contributes to their infertility, but assessment of the impact of multiple diagnoses and their severities was simplified by the availability of the previously validated combined diagnostic severity score. This study was also able to use the same area-based measure of SES as the population survey (the deprivation index), thereby providing unique insights into infertility care by SES in New Zealand.

7.3.3 Limitations of the population-based survey

The survey had a modest response rate of 60.1%, with lower response rates in sub-groups with a slightly lower prevalence of infertility. Also, those who were younger and those more deprived were less likely to be in the survey's sampling frame (the electoral roll). However, the estimates of infertility from a Dunedin-based cohort study with very high retention rates and the measure of childlessness from the New Zealand census were all very similar to the survey results, suggesting that potentially the impact of selection bias may not have been severe.

There is some evidence that recall of detailed fertility events may not be very accurate; van Roode *et al.* (2015) found discrepancies between infertility reports in a birth cohort that was questioned at ages 32 and 38. This found some infertility events that were reported at age 32 were not reported when participants were asked about all post infertility events at age 38. To reduce information bias in this cross-sectional study, infertility was measured using both a fertility history method and specific questions on infertility. Women not self-defining as having had difficulties conceiving, but who had taken longer than 12 months to conceive a pregnancy, were included as infertile. Whilst the measure of infertility prevalence could not be compared with findings from the clinic data, diagnoses, treatment uptake and resolution after seeing a specialist could all be compared. The two

datasets were very similar; no evidence of strong information bias in the survey participants' data was detected.

As the study was of a cross-sectional design, important factors that influence infertility such as age, BMI and smoking were ascertained either during the current experience of infertility or after the experience of infertility. It is unknown for BMI and smoking whether this measurement reflects their status prior to experiencing infertility. For BMI in particular, reverse causation could be an issue; women may increase in BMI after having a child, therefore measuring BMI after having children may mask the effect of BMI on infertility and resolution of infertility.

7.3.4 Limitations of the clinic-based study

As the underlying prevalence of infertility in the population is unknown, there was little evidence to assess whether clinic access was equitable by such characteristics as ethnicity and deprivation across the Otago and Southland regions.

Despite the large sample size, the clinic-based study lacked power to investigate differences by ethnic group. Furthermore, loss to follow up could be related to the likelihood of resolution of infertility, which would introduce selection bias. It would have been useful to have more details about reason for withdrawal to assess this. However, competing risk analysis, which controlled for the effect of relationship separation (one of the withdrawal categories) preventing resolution from occurring, provided very similar results to a standard Cox's regression. Thus, no evidence of strong bias due to withdrawal because of separation was detected.

7.3.5 Limitations of the analysis of the national hospital discharge data

Serious limitations were encountered when using the hospital discharge data, especially when interpreting the PID trends. PID diagnosis is subjective and possibly inaccurate. Furthermore, it is also likely that, especially for asymptomatic PID, the majority of cases remain undiagnosed, and the remaining cases are more likely to be treated in the community and not as hospital inpatients (refer to Section 6.1.3, pages 205–207, for a more detailed discussion on the limitations of using hospital discharge data for these conditions). The underlying patterns of

health care access by various groups (e.g. by ethnicity and/or deprivation) would be likely to influence rates of diagnosis. So, higher levels of hospitalised care could reflect more severe forms of disease, or less access to primary health care resulting in worse disease progression and higher use of hospital services. Similar limitations apply when interpreting infertility diagnoses, although there is not likely to be the same level of inaccuracy in the diagnosis. Also, there is not a good denominator; not all women are at risk of infertility. Furthermore, of those that choose to use infertility services in New Zealand, around half opt for privately funded treatment (Peek, 2015), and privately funded hospital admissions could not be included in this analysis due to limitations of the national dataset.

7.4 Interpretation of main findings

The Otago and Southland regions of New Zealand appear to have relatively high infertility, but also high and reasonably equitable service access. These findings from the population-based study, along with the infertility prevalence estimate provided by van Roode *et al.* (2015), are the only population-based estimates of infertility in New Zealand.

Despite this equitable service access, findings from the two infertility studies in this thesis conversely demonstrate that resolution of infertility was *not* equitable, being associated with such measures as deprivation, relationship status, BMI and treatment uptake. Furthermore, clinic-based data also showed that withdrawal from infertility care was more common amongst women who are known to have worse health outcomes in general in New Zealand; those suffering from higher deprivation and those of Māori ethnicity. These models, demonstrating the adjusted risks for resolution of infertility and withdrawal from infertility care offer insights into how some groups of women may be benefiting from infertility care less than others. Whilst the results for these models were not unpredictable, they provide confirmation of these suspected inequitable outcomes. Further research is particularly needed to determine the mechanism by which SES is impacting in resolution of infertility and to ascertain why some women/couples withdraw from care before the conclusion of their programme.

Age was found to be an important predictor of receiving treatment and, for both studies, the likelihood of infertility resolution; being of older ages was more detrimental to success. The thesis results confirm that, alongside age, one of the other important physiological factors impacting of infertility for women is BMI, with high BMI predicting increased risk of infertility and ovulation disorder being the most common diagnosis for infertile women. Women with very high BMIs were also more likely to withdraw from infertility care and less likely to receive treatment, some of this negative impact of high BMI is likely to be explained by ineligibility for public funding. Thus, the increasingly important role of age and BMI in infertility and resolution of infertility found in previous research was also confirmed for women in Otago and Southland.

Relationship status also predicted infertility, with those not in a heterosexual relationship less likely to experience infertility. However, patients in the clinical study were less likely to resolve their infertility if they were not in a heterosexual relationship. Reduced SES (deprivation, education and income measures for these studies) was associated with slightly less service access (for income and education measures), increased withdrawal from care (with increasing deprivation) and with reduced resolution of infertility (with increasing deprivation) in both studies. Within the clinic-based study diagnostic severity and treatment were also very important predictors of successful resolution of infertility. Previous studies have concluded that women who received infertility treatment were as likely or less likely than women who had no treatment to resolve their infertility (Buckett and Bentick, 1997, Bhattacharya *et al*., 2009). By analysing infertility resolution using regression modelling and controlling for the confounding effects of such factors as diagnostic severity, the beneficial effect of treatment was confirmed by this research.

Infertility knowledge was generally poor amongst the survey participants; this finding was in common with previous research in this field. This is of particular concern given that the impact of the region's high levels of infertility could perhaps have been mitigated by women/couples having the appropriate knowledge to make informed choices about their future fertility. Of further concern was that a

high proportion of women were undertaking ovulation monitoring despite having poor fertility knowledge, suggesting that they could have implemented this in such a way that it was detrimental their ability to conceive.

7.4.1 Generalisation of research to other regions in New Zealand

Whilst one further population-based study in New Zealand exists, this was in the same region as these thesis studies, not allowing for a wider comparison to be made. The national hospital discharge data suggested differences in reproductive health between the Otago and Southland regions and the rest of New Zealand; however, the value of hospitalisation data for informing population trends is debatable. The survey data suggest slightly lower rates of infertility amongst women of Māori descent and those from more deprived neighbourhoods, both of which are less common in Otago and Southland than nationally in New Zealand. This would suggest infertility and service access measures may be higher in these regions and not generalisable to the rest of New Zealand. But, it is likely that findings regarding the importance of age, BMI, male factor infertility and SES will be common to the rest of New Zealand, though the relative importance may vary.

7.4.2 Generalisation further afield

Measures of infertility prevalence and service use vary, as would be expected, by country. As such, these measures are useful and intended for local analyses/application and comparisons, and could perhaps be broadly generalised to other high-income countries with similar fertility patterns. However, the models that determine likelihood of infertility resolution could usefully be applied to populations with a similar socio-economic background and fertility patterns in the absence of good local data. Furthermore, findings on the determinants of infertility, service seeking and resolution add to and support the findings in other high-income countries.

7.4.3 Implications for policy, clinicians and the public

In a country with delayed childbearing, such as New Zealand, the prevention of infertility should be targeted using strategies to reduce the delay in parenthood. This would reduce the likelihood of infertility, and thereby stress on services and individuals, and allow sufficient time to ensure that desired family size can be attained. Strategies that successfully reduce the delay in parenthood would also likely offset the longer-term potential risk to the community and economy of negative population growth.

Possible strategies could include social media campaigns, targeting primary care and secondary and tertiary education providers. To date, there are no evidence-based strategies for reducing the delay in parenthood, either in New Zealand or in other countries. Therefore, should potential strategies/policies be developed and implemented, it would also be extremely valuable if their implementation included a plan for formal assessment of the impact of the intervention. Policies that provide cash incentives for having children and reduce the cost of childcare are already in place in New Zealand, but the effect of the implementation of these policies on the median age of childbirth has not been assessed.

Fertility awareness advice is particularly important and needs more emphasis, especially at the primary care level. One possible strategy to further this could be the development of software applications to guide care, targeted at both primary care clinicians and women/couples intending to conceive. Alongside this, given the popularity of ovulation monitoring, more needs to be done to provide women with the required knowledge and skills so that such practices do not become detrimental to their ability to conceive and add further stress. Results from this thesis support the recommendation by Society for Assisted Reproductive Technology (2012) that couples should have regular rather than timed intercourse. Further assessment of the impact of ovulation monitoring and timed intercourse on time to pregnancy is needed before reconsidering recommended this practice.

The information provided by the clinic-based study's models of treatment uptake and resolution of infertility is rare and, in particular, will be valuable for patients and clinicians when assessing a patient's likelihood of being able to have a child in the future. Further information is required on withdrawal from infertility care to facilitate better outcomes for these women and reduce unnecessary cost to the health service. The study results suggest that having an unhealthy BMI leads to higher levels of withdrawal, this may be due to the non-treatment management of patients, and that resolution of infertility was still relatively common amongst women who had a BMI above the cut off for receiving publicly funded ARTs. Most countries with formal policies regulating the provision of ARTs have age limitations, but few have formal limitations based on BMI (Dunne *et al*., 2014); it may be that BMI restrictions in New Zealand should be reconsidered and, alternatively, assessed on a case-by-case basis by infertility specialists.

While the results from studies in this thesis did not suggest that smoking or STIs were significant contributors to infertility risk, it is still important to consider reducing these highly modifiable fertility risks. The burdens of these fertility risk factors, and that of obesity, are disproportionately distributed, being much higher amongst Māori, who were not strongly represented in this research. New Zealand already has a formal target of being a smoke free nation by 2025 (Smoke Free Coalition, 2010) and strong smoke free legislature; however, there has been little leadership from the government in tacking STIs or obesity. Despite having sexual education at secondary schools and very good levels of testing for C. *trachomatis* due to opportunistic screening, this STI remains very common (The Institute of Environmental Science and Research Ltd., 2012) and it may be that the only plausible method of control would be the development of an effective vaccine; international research is currently focussed on this issue. Tacking obesity could take a similar form to tobacco control: Taxation of unhealthy foods (potentially allowing for subsidising fresh fruit, vegetables, lean meats and fibre-rich foods); marketing and sponsorship restrictions; and only allowing approved food types to be displayed (and perhaps sold) in work place and school canteens. Furthermore, the development of infrastructure to allow and encourage safe alternative transportation such as cycling would also have an impact on obesity and overall

fitness. However, currently the New Zealand government appears to be reluctant to take such measures.

7.4.4 Implications for research

Further research is needed at a national level in New Zealand, or in other regions outside of Otago and Southland, to: a) validate the findings of this thesis; b) provide more information about the impact of ethnicity on withdrawal, treatment uptake and infertility resolution; and c) to determine the mechanisms by which SES is impacting on resolution of infertility. For those women with unresolved infertility but not accessing care, more research is needed to determine whether there is a service gap that requires addressing, this may, for example, be related to access to services for people in remote location or the provision of culturally appropriate services.

A national Ministry of Health survey, investigating sexual and reproductive health, is currently underway and will provide basic national data on the prevalence of infertility. This may allow for further assessment of whether more detailed infertility results from the studies in Otago and Southland can be further generalised.

Age, BMI and specific clinical information such as severity of diagnosis, have long been known to impact on infertility and infertility related outcomes such as resolution of infertility. However, BMI limits for public funding of treatment are the same for all women in New Zealand; although the maximum threshold for treatment was raised from 30 to 32 kg/m^2 to take into account ethnic differences in healthy BMI, the blanket application of this threshold might disadvantage Māori and Pacific Islanders who have higher BMIs for the equivalent body fat percentage compared with Europeans (Rush *et al.*, 2007). The impact of higher BMIs on infertility amongst these populations needs further research to determine if the criteria for funding need to be adjusted (or removed). As with SES, the role of relationship status needs further research. The role of male factor infertility and the impact of this on men and relationships also warrant more focus given that

semen disorder is one of the leading causes of infertility. A prioritised research agenda to address these knowledge gaps in New Zealand is set out in Table 7.1.

Table 7.1: Suggested research agenda to address infertility knowledge gaps in New Zealand*

Knowledge gap	Suggested research
Validation of the thesis findings on the experience of infertility, services use, and resolution of infertility at a national level.	The current national survey by the Ministry of Health may do this if the overall findings are similar. However, if the findings are very different a national survey equivalent to that undertaken in this thesis will be required to understand infertility across New Zealand.
More information needed on the impact of ethnicity on withdrawal, treatment uptake and infertility resolution.	A mixed methods study with cognitive interviews from patients who have completed infertility treatment and patient's who withdrew may be needed to supplement potential clinic information from North Island fertility clinics (should quantitative data be available). If quantitative data on patients were not available, a cohort study following patients from at least one clinic, preferably in Auckland, would be most valuable.
The effect of high BMI on fertility and infertility resolution needs assessed by ethnic group.	Data and/or a cohort study, as mentioned above with, data/patients from an Auckland clinic would have the potential to further investigate the effect of BMI on fertility in populations with higher healthy BMIs. It is likely that the current funding and treatment options for those with high BMI will impact of withdrawal from service, so it would be more efficient, and yield better data, if BMI and withdrawal were studied simultaneously.
Assessment of service provision for women with unresolved infertility who have not sought medical help.	Should a national survey, or other regional surveys, take place, questions should be included regarding why infertile women/couples have not sought help. The development and piloting of these questions would likely require qualitative interviews with women who have experienced infertility. Infertility clinic data could also be investigated for location identifiers to see if access issues (such as rural residential address) impact on withdrawal. If this were the case, it would suggest that this might also impact on initial service seeking.
The effect of SES on infertility resolution needs explored.	Potentially, a prospective case control study could used to examine SES along with other potential determinants; however, the controls (women who did not resolve their infertility) may be very difficult to define and enrol.

* *Listed in order of priority.*

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APPENDIX A: METHODS AND METHODOLOGICAL ISSUES OF REVIEWED STUDIES

Studies measuring the prevalence on infertility

Study design strengths and limitations

In addition to the general strengths and limitation of cross-sectional design that were discussed in Section 2.5.1 on page 25, the various methods of data collection also have associated strengths and limitations. Using interviewers will be relatively more expensive than postal questionnaires, but may lead to questions being answered more accurately (as the participant can seek clarification), the correct questions being completed (especially for complex pregnancy histories) and may lead to better response rates (see below). However, a self-completed questionnaire will exclude the possibility of interviewer biases that may arise should an interviewer unwittingly lead a participant towards a particular answers based on the interviewers preconceived notion of what the answer should be. Self-completed questionnaires, for personal health questions in particular, may also lead to less social desirability bias (whereby a participant may alter their answer to a question according to what they believe the interviewer and/or society in general find most socially acceptable) and less concerns regarding anonymity and privacy for the participant.

Low response rates are now common in cross-sectional studies and can be a very serious limitation. Whilst comparisons can be made with demographic factors in the population to determine representativeness, in reality there is very little information that can be used to determine how these low response rates are influencing the prevalence measure in infertility studies.

In addition to the general limitations of the cross-sectional design, there are also difficulties with the nature of infertility. Until women test their fertility they are unlikely to know that there are issues, so diagnosis may occur well after onset,

especially in middle to high-income countries. Also, studies have reported that the majority of women do not perceive infertility to be a medical condition (Fuentes and Devoto, 1994, Adashi *et al.*, 2000), therefore, many women may not identify themselves as *infertile*. The perceptions, knowledge, and therefore advice given by health professionals, also vary. Even if a meaningful definition was clearly established reproductive histories are often complicated, and asking a woman to accurately recall her sexual behaviour, contraceptive use and pregnancy history up to thirty or more years ago will inevitably have inaccuracies.

Definitions of infertility employed

There was considerable variation in the definition of infertility used in the reviewed studies, and how information was gathered for the definition. The most recent accepted epidemiological and clinical definition, as mentioned earlier, is attempted conception for 12 months or more (irrespective of whether a pregnancy occurs after 12 months), using the specific wording *trying* and often referred to as *trying times* (Larsen, 2005, Gurunath *et al.*, 2011). However, the World Health Organization has published a variation of this definition which is more encompassing, being '12 months or longer of regular unprotected intercourse without conception' (Zegers-Hochschild *et al.*, 2009). Most studies have used variations of these two definitions, although some use a two-year duration, which was historically more common.

The use of time spent trying to conceive has the advantage of including the intention to get pregnant in the definition. Women who are not using contraception are not necessarily trying for or even wanting a pregnancy. Therefore, if a study aims to look at emotional/psychological burdens associated with infertility and/or service needs for infertility, it would be most appropriate to use time spent trying to conceive. Another advantage of this definition is that women who are actually trying to conceive will be more likely to accurately remember how long they were trying for. However, if a study is looking at risk factors for infertility, then associations may be masked if women who are possibly infertile (even though they did not have any intention to get pregnant) are not included as cases. So, with the exception of single and/or lesbian women who are

trying to conceive, for an analytical study it would be better to use a definition of non-contracepting with regular intercourse. Generally it is now accepted, especially in middle to high-income countries, that the best duration to use is 12 months. However, as women tend to seek clinical help earlier these days (Wilkes *et al.*, 2009), using a duration of longer than 12 months could underestimate the health-care and psycho-social burdens associated with infertility.

While the definition used by various studies was quite clear, which question(s) were used in order to derive the defined infertility state was not always explicit. Looking at postal questionnaires first, some surveys used a gateway question like 'Have you and your partner (current or previous) ever had problems with infertility?' (Herbert *et al.*, 2009b). This was usually followed by duration question(s). A simplified method using only one question to meet the definition, 'Did you ever try to get pregnant for more than 1 year without success?' or similar, was used in four studies (Sundby and Schei, 1996, Wyshak, 2001, Clark and Mackenzie, 2007, Terava *et al.*, 2008). Other surveys used a pregnancy history approach, but not all of these included a time to conception measure (Templeton *et al.*, 1990, Templeton *et al.*, 1991, Gunnell and Ewings, 1994, Oakley *et al.*, 2008, Bhattacharya *et al.*, 2009). Some studies such as that conducted by Wyshak (2001), had results that were not inclusive of all infertile women; in this study they did not consider women who eventually had a non-treatment related pregnancy as meeting their definition.

Pregnancy history and infertility questions can be difficult to succinctly word in a way that will be both meaningful to the majority of women, yet capture sufficient and accurate information. Some of the questions and questionnaire structures previously employed could have been confusing or inadequate. One study compared results in a sub-sample from their postal survey respondents with their GP records and with a sample of the non-responders (Gunnell and Ewings, 1994). It found evidence that the self-completed postal survey introduced some information and response bias. There were discrepancies with self-reports in both directions. A number of women had not self-reported infertility investigations that were in their GP notes, but there were also a few women who had self-reported

infertility but there was no supporting evidence from their GP (although they may not have sought medical help or sought help elsewhere, so this is not conclusive). Based on their GP records, rates of primary infertility between responders and non-responders were similar, but non-responders were more likely to have consulted a GP for secondary infertility and have been referred for a termination of pregnancy. The information bias may have arisen due to unclear questions, or also due to recall issues. One other study compared self-reported infertility with a reproductive control indicator, built from known pregnancies, to gauge the accuracy of self-reported infertility. Self-reported infertility of 12 months or longer had high specificity (94.8%), but a lower sensitivity (63.4%). The sensitivity may have been influenced by whether a woman had had a live birth (Geelhoed *et al.*, 2002). The evidence from these two papers suggests that when women report infertility this is likely to be correct, but there may be a number of women who have experienced infertility but do not report this, this method will result in an estimate of infertility that is lower than the actual prevalence.

Many of the studies done by face-to-face interviews were not explicit about how the interview was structured, although pregnancy histories, contraceptive use, reproductive health and service seeking were common themes. In low-income countries the definition of infertility was generally built around a scenario of not contracepting and not conceiving following marriage (Fuentes and Devoto, 1994, Liu *et al.*, 2005, Ahmadi Asr Badr *et al.*, 2006, Safarinejad, 2007, Vahidi *et al.*, 2009). The general assumption in most of these studies is that women who are not contracepting and are married will be intending to get pregnant due to the cultural desirability of children. In the two most recent studies set in middle to high-income countries using face-to-face interviewing, the structure of the interview and construction of the infertility definition was not clear (Stephen and Chandra, 2006, Klemetti *et al.*, 2010).

Denominator for calculating the prevalence of infertility

Many studies had a sampling frame that included either all women or married women, and this was used for the denominator for calculating the prevalence of infertility (refer to Tables 2.1 on page 37 and 2.2 on page 42 for details of

denominators used for each reviewed study). However, not all women/all married women would have been at risk of infertility, this will lead to the prevalence of infertility being underestimated. Schmidt *et al.* (1995) reported in their study that including all women in the denominator substantially reduced the measured prevalence of infertility from 26.2% to 15.7%; the denominator differences were most noticeable in women under the age of 35 years. A more appropriate denominator has been argued to be women who have either conceived or have tried to conceive when using the 'time spent trying' definition (Gurunath *et al.*, 2011); a number of studies used this approach. For the World health Organization definition the corresponding denominator (including only women at risk) should be women who have conceived or not used contraception whilst having regular intercourse.

Age groups assessed

There was considerable variation in the age ranges assessed in studies set in middle to high-income countries. These can be grouped into four sets of age categories:

- Women who were peri- or post-menopausal and likely to have completed their fertility (Rostad *et al.*, 2006, Herbert *et al.*, 2009a).
- Women who were in their latter reproductive years and/or menopausal and may have completed their childbearing (aged over 40) (Templeton *et al.*, 1990, Sundby and Schei, 1996, Buckett and Bentick, 1997, Oakley *et al.*, 2008).
- Women who were likely to be currently planning or having children in middle to high-income countries (aged over 25 years) (Templeton *et al.*, 1991, Gunnell and Ewings, 1994, Karmaus and Juul, 1999, Mohsen *et al.*, 2001, Greil and McQuillan, 2004, Bhattacharya *et al.*, 2009, Herbert *et al.*, 2009b, Klemetti *et al.*, 2010).
- Studies that, similar to those in low-income countries, covered the full reproductive life span (Webb and Holman, 1992, Schmidt *et al.*, 1995, Philippov *et al.*, 1998, Stephen and Chandra, 2006, Clark and Mackenzie, 2007, Slama *et al.*, 2008, Terava *et al.*, 2008).

As planned pregnancies generally occur later in middle to high-income countries when compared with low-income countries, even for measuring current infertility, it is appropriate to look at women of an older age group. However, fertility patterns vary by age and ethnicity within these countries, and, in order to elucidate these patterns, especially for current infertility, a wider age range (and larger sample) may be required. If a total measure of the lifetime experience of infertility is required, then it is necessary to examine women who are likely to be no longer fertile, and a few studies have done this by limiting the age group to women who are likely to be peri or post-menopausal. But, another possible approach is to include older women in a broader study and then stratify the study data by age.

Due to the highly variable age ranges in the studies undertaken in middle to high-income countries, prevalence comparisons can be difficult and must be made cautiously.

In low-income countries, for both studies on current and lifetime experience of infertility, the age groups for the studies covered women in their reproductive years. Apart from one study in China on women aged 15–57 years (Liu *et al.*, 2005), these studies did not include women likely to be post-menopausal. All of the other studies were approximately in the age range 15–49 years, although one included slightly older women in Gabon with ages 15-54 (but limited to menstruating women) (Schrijvers *et al.*, 1991).

All but four studies from low-income countries exclusively measured the current experience of infertility; therefore, the selected age range would have excluded most post-menopausal women. In general, childbearing is socially desirable, and occurs more frequently, at younger ages compared with more middle to high-income countries. Therefore, the younger age ranges studied were culturally and methodologically appropriate.

Studies evaluating service use for infertility

Population-based epidemiological studies of infertility

Many cross-sectional surveys on infertility included measures of service access and a few also looked at treatment provision and outcome. Unfortunately, most studies that investigated service use in low-income countries were based on fecundity measures and were, therefore, not able to be included in the literature review, resulting in only one population-based study from a low-income country.

Data were diverse and difficult to compare due to differences in populations, time and definitions of infertility as already described. The definitions for service access, treatment and outcome also need to be considered.

Service access was measured using varying definitions. Some studies specifically asked about access to medical services, e.g. 'Have you ever seen your GP or hospital doctor about any difficulty in becoming pregnant?' (Bhattacharya *et al.*, 2009), 'Did you consult a physician?' (Moreau *et al.*, 2010), '...ever used fertility services?' (Chandra and Stephen, 2010) and 'Did you ever seek medical treatment for infertility?' (Wyshak, 2001). The level of access (primary, secondary or tertiary service) was either not specified, or varied between these studies. Two studies specified the level of access to medical services and were, therefore, able to look at proportions of women being referred to more specialist services (Gunnell and Ewings, 1994, Buckett and Bentick, 1997). Some studies did not specify how service access was measured or defined (Clark and Mackenzie, 2007), and had very non-specific questions such as that used by Herbert *et al.*: (2009) 'did you seek advice/treatment?' (Herbert *et al.*, 2009b).

Wyshak (2001) had service use results that were particularly difficult to interpret. The study methods stipulated that participants were asked about 'seeking treatment' and then in the results Wysak seemed to consider that all women who sought treatment had then received treatment. This result has been included in the literature review as seeking rather than receiving treatment for infertility. Their results may also be an over-estimate of treatment seeking as they include women

who tried for more than 12 months, but had spontaneous pregnancies without seeking treatment. However, there was no category for women who had unresolved infertility of 12 months or more and did not seek treatment.

Treatment uptake was not possible to compare between these studies as what was included as 'treatment' was diverse and in one case the definition of treatment was not specified at all (Herbert *et al.*, 2009a). Also, only three epidemiological studies gave an indication as to whether the infertility was spontaneously resolved, resolved following treatment or unresolved (Schmidt *et al.*, 1995, Buckett and Bentick, 1997, Bhattacharya *et al.*, 2009). Gunnell and Ewings (1994) reported whether infertility was resolved or unresolved, but did not specify whether this was following medical treatment.

Clinic-based epidemiological studies of infertility

All but one of the studies were based on an analysis of routine records held by GPs and/or tertiary infertility services (refer to Table 2.3). Studies based in a clinical setting have the disadvantage of not being able to give information about the proportions of infertile women who access services, but have the advantage of providing information on diagnoses, treatment and outcomes free from issues such as recall bias.

Studies evaluating service use for infertility

Population-based epidemiological studies of infertility

As discussed previously in Section 2.5.2 on page 28, service access was measured using varying definitions. Some studies specifically asked about access to medical services, e.g. 'Have you ever seen your GP or hospital doctor about any difficulty in becoming pregnant?' (Bhattacharya *et al.*, 2009), 'Did you consult a physician?' (Moreau *et al.*, 2010), '...ever used fertility services?' (Chandra and Stephen, 2010) and 'Did you ever seek medical treatment for infertility?' (Wyshak, 2001). The

level of access (primary, secondary or tertiary service) was either not specified, or varied between these studies.

Wyshak (2001) had service use results that were particularly difficult to interpret. The study methods stipulated that participants were asked about 'seeking treatment' and then in the results Wysak seemed to consider that all women who sought treatment had then received treatment. This result has been included in the literature review as seeking rather than receiving treatment for infertility. Their results may also be an over-estimate of treatment seeking as they include women who tried for more than 12 months, but had spontaneous pregnancies without seeking treatment. However, there was no category for women who had unresolved infertility of 12 months or more and did not seek treatment.

Studies in infertility knowledge and attitudes

Middle to high-income countries

Further to the overview of the knowledge studies given in Section 2.5.3 on page 29, five of these were surveys amongst academics or tertiary students (Kuang *et al.*, 2006, Lampic *et al.*, 2006, Bunting and Boivin, 2008, Rovei *et al.*, 2010, Virtala *et al.*, 2011) and one was amongst secondary students (Quach and Librach, 2008). One study was a population-based survey of childless women (Daniluk *et al.*, 2012). Just two studies were population-based samples covering a wide range of ages (Adashi *et al.*, 2000, Clark and Mackenzie, 2007). There were a further two knowledge surveys amongst women attending clinics for infertility services (Blake *et al.*, 1997, Vause *et al.*, 2009).

The survey instruments and style of questions varied significantly between studies. Two surveys used questionnaires that asked whether participants agreed with a statement e.g. 'Being underweight or overweight can put me at risk of being infertile.' Using either a yes/no approach or a Likert scale, the authors then calculated the proportions of correct answers for each question (Quach and Librach, 2008, Daniluk *et al.*, 2012).

Researchers in Finland and Italy used variations of the following open-response questions: 'At what age is there a slight decrease in a woman's ability to become pregnant?'; 'At what age is there a marked decrease in a woman's ability to become pregnant?'; and 'If a man and a woman regularly have unprotected intercourse during a period of one year, how high is the chance (%) that the woman will become pregnant if she is: (a) 25–30 years old? (b) 35–40 years old?' (Rovei *et al.*, 2010, Virtala *et al.*, 2011). Rovei *et al.* (2010) also looked at knowledge regarding treatment success and legislation regarding ART in Italy, and the frequency of conception on a monthly basis. Questionnaires from these two studies were based on an earlier survey in Sweden by Lampic *et al.* (2006), although their responses were in a multi choice format.

Bunting and Boivin (2008) had a unique approach of asking participant's to estimate the effect of a factor on the fertility of 100 women trying to get pregnant; participants could reduce or increase the chances of pregnancy (of leave unchanged) for each factor. They then grouped their questions into 'risk factors', 'fertility myths' and 'healthy habits' to generate grouped knowledge scores.

In one of the earliest studies, Adashi *et al.* (2000) used a very short telephone-based survey in multiple countries to assess public knowledge regarding the definition of infertility, whether infertility is perceived as a disease, the levels of infertility and likelihood of treatment success with IVF.

In general, these studies were not explicit about recruitment or sample sizes, and often did not report response rates, so the likelihood of these data being representative is difficult to determine. However, of 10 studies only three were population-based (Adashi *et al.*, 2000, Clark and Mackenzie, 2007, Daniluk *et al.*, 2012), with the remaining being either in secondary/tertiary education (Kuang *et al.*, 2006, Lampic *et al.*, 2006, Bunting and Boivin, 2008, Quach and Librach, 2008, Rovei *et al.*, 2010, Virtala *et al.*, 2011), or amongst clinic attenders (Blake *et al.*, 1997, Vause *et al.*, 2009). Therefore, these studies are unlikely to be representative of the general population.

Of the two clinic-based surveys identified, the more recent was in Canada by Vause *et al*. (2009) and an earlier study was in New Zealand by Blake *et al*. (1997). Both of these studies enrolled tertiary infertility service attenders, inviting them to complete a knowledge survey prior to their appointment. Both studies were in women only and neither reported their response rates. Blake *et al.* (1997) gave a more detailed report on their questionnaire structure; this was focused on knowledge of the fertile time period, including questions on symptoms of cyclic fertility such as changes in cervical mucus. Responses were almost exclusively in a multi-choice format.

Low-income countries

The only study from a low-income country included in the literature review was based in Pakistan. This was a population-based survey of adults accompanying patients to hospital looking at knowledge and attitudes regarding infertility and infertility treatment. The questions used and style of answer was not stated (Ali *et al.*, 2011). The study had an excellent response rate of 97%.

APPENDIX B: COMPUTERISED QUESTIONNAIRE

[Page 1: Introduction]

Thank you for logging in to complete this confidential questionnaire.

If you have any questions please contact Antoinette Righarts (researcher at the Dunedin School of Medicine): e-mail antoinette.righarts@otago.ac.nz or telephone (03) 477 0454.

Please answer all sections. It takes between 10 and 15 minutes.

Please enter your survey password: _____

[Error message for incorrect password: "That password is incorrect. Please check that you have typed out the password exactly how it is shown on your invitation letter (make sure you have used lowercase letters). If this does not work, please contact Antoinette. Thank you."]

[Page 2: Section 1, fertility experiences] [Show questions 1 & 2]

1. How old are you? _____ years

2. Have you ever been pregnant? ☐ Yes [show q3 &4] ☐ No

3. Are you currently pregnant? ☐ Yes ☐ No

4. How many times have you previously been pregnant?* *Not including your current pregnancy (if applicable*)
   ☐ None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
   ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 or more [show q5]

[q4 sets loop number and counter for q6]

5. You responded that you have been previously pregnant 10 or more times, what is your total number of previous pregnancies? *Not including your current pregnancy (if applicable)* _____ [10–40 valid]

[Page 3: Section 1, continued] [Show page if q4>0] [Show questions 6, 6a, b & u]

6. [If (q4>1 & q4<5 & q3="yes") or (q4=5 & q5=5 & q3="yes"): "This series of questions will be asked for each of the **[q4] times** you have been pregnant, starting with your earliest pregnancy. Then questions will be asked about your current pregnancy."] [If (q4>1 & q4<5 & q3="no") or (q4=5 & q5=5 & q3="no"): "This series of questions will be asked for each of the **[q4] times** you have been pregnant, starting with your earliest pregnancy."][If q4=5 and q5>5: "This series of questions will be asked for each of the **first ten times** you have been pregnant, starting with your earliest pregnancy. Then we will ask you briefly about all of your subsequent pregnancies."] [If q4=1 & q3="yes": "These questions are about the **one time** you have previously been pregnant. Then questions will be asked about your current pregnancy."]

Pregnancy [q4 loop no]:

a) How old were you when you got pregnant? _____ years

b)	What was your relationship status when you got pregnant? [If options 1 – 2 show d, options 3 – 5 show c]	☐ Married or living with a male partner ☐ Male partner but not living together ☐ Civil union or living with a female partner ☐ Female partner but not living together ☐ Not in a relationship
c)	How did you get pregnant?	☐ A male partner who I was not in a relationship with ☐ I received medical help ☐ Other, please specify_____
d)	Were you trying to get pregnant?	☐ Yes [show f] ☐ No [show e]
e)	Were you having regular intercourse without using any methods to avoid pregnancy?	☐ Yes [show u] ☐ No
f)	Did you have any difficulties getting pregnant (or did you need medical help to get pregnant)?	☐ Yes [show g & h] ☐ No [show t]
g)	Did you see a GP, family planning or other non-specialist doctor about your difficulties?	☐ Yes [show j, k & s] ☐ No [show i]
h)	Did you see a non-medical health provider about your difficulties? E.g. naturopath, homeopath, acupuncturist, traditional healer or educator	☐ Yes ☐ No
i)	Did you see a fertility specialist or a gynaecologist?	☐ Yes [show j, n, o & s] ☐ No [show t]
j)	How long had you been trying to get pregnant when you saw that doctor?	☐ I saw the doctor before I started trying ☐ Up to 6 months ☐ 6 – 11 months ☐ 1 – 2 years ☐ Over 2 years
k)	What help did your doctor provide? *Tick all that apply* [If "referral" show l]	☐ Advice ☐ Testing, please specify_____ ☐ Referral to a fertility specialist ☐ Referral to general gynaecologist ☐ Other, please specify_____ ☐ No help was provided
l)	Did you get pregnant before seeing the specialist?	☐ Yes ☐ No [show m, n & o]
m)	How long did you wait to see a specialist after getting referred?	☐ Less than 1 month ☐ 1 – 6 months ☐ Over 6 months
n)	Were any reasons found that explained why you were experiencing difficulties? *Tick all that apply*	☐ Ovulation problems ☐ Blocked fallopian tubes ☐ Endometriosis ☐ My partner had sperm problems ☐ I have unexplained infertility

		☐	Other, please specify _____
o)	Did you receive any of these treatments? *Tick all that apply* [If "IVF" show p & q, if "AI" show q, if options 1 – 5 show r]	☐ ☐ ☐ ☐ ☐ ☐	Drugs to improve ovulation Artificial insemination IVF (In vitro fertilization) Surgery Other, please specify _____ N/A, I got pregnant before starting any treatment
p)	Who provided the egg(s) for IVF?	☐ ☐ ☐	Myself Anonymous donor Known donor
q)	Who provided the sperm?	☐ ☐ ☐	My partner Anonymous donor Known donor
r)	Did this pregnancy occur as a direct result of your treatment?	☐ ☐ ☐	Yes No Not sure
s)	From the time you first started trying, how long did it take you to get pregnant? *Include time spent getting medical help*	☐ ☐ ☐ ☐	Up to 6 months 6 – 11 months 1 – 2 years Over 2 years
t)	From the time you first started trying, how long did it take you to get pregnant?	☐ ☐ ☐ ☐	Up to 6 months 6 – 11 months 1 – 2 years Over 2 years
u)	How long were you having regular intercourse (without using methods to avoid pregnancy) before you got pregnant?	☐ ☐ ☐ ☐	Up to 6 months 6 – 11 months 1 – 2 years Over 2 years
v)	How did your pregnancy end?	☐ ☐ ☐ ☐ ☐ ☐	Live birth Stillbirth Miscarriage Termination (Abortion) Ectopic (tubal) pregnancy Molar pregnancy

[Page 4: Section 1, continued] [Show page if q5>10] [Show questions 7, 7a if q5=11, 7b if q5>11, 7d & 7e if q3 not "yes"]

7. These questions are about **all of your subsequent pregnancies** (all pregnancies after your tenth pregnancy).

For any of your subsequent pregnancies:

a)	Did you spend 12 months or more trying to get pregnant?	☐ ☐	Yes No [show c]
b)	Did you ever spend 12 months or more trying to get pregnant for any one of these pregnancies?	☐ ☐	Yes No [show c]

c)	Did you ever have regular intercourse without using any methods to avoid pregnancy for 12 months or more before you got pregnant?	☐ Yes ☐ No
d)	Did you ever seek medical help to get pregnant?	☐ Yes ☐ No
e)	How old were you when you **last** got pregnant?	_____ years

[Page 5: Section 1, continued][Show page if (q3="yes" & q4<10) or (q3="yes" & q4=10 & q5=10)][Show questions 8 & 8a]

8. These questions are about your **current** pregnancy.

a)	What was your relationship status when you got pregnant? [If options 1 – 2 show c, if options 3 – 5 show b]	☐ Married or living with a male partner ☐ Male partner but not living together ☐ Civil union or living with a female partner ☐ Female partner but not living together ☐ Not in a relationship
b)	How did you get pregnant?	☐ A male partner who I was not in a relationship with ☐ I received medical help ☐ Other, please specify_____
c)	Were you trying to get pregnant?	☐ Yes [show e] ☐ No [show d]
d)	Were you having regular intercourse without using any methods to avoid pregnancy?	☐ Yes [show t] ☐ No
e)	Did you have any difficulties getting pregnant (or did you need medical help to get pregnant)?	☐ Yes [show f & g] ☐ No [show s]
f)	Did you see a GP, family planning or other non-specialist doctor about your difficulties?	☐ Yes [show i, j & r) ☐ No [show h]
g)	Did you see a non-medical health provider about your difficulties? E.g. naturopath, homeopath, acupuncturist, traditional healer or educator	☐ Yes ☐ No
h)	Did you see a fertility specialist or a gynaecologist?	☐ Yes [show i, m, n & r] ☐ No [show r]
i)	How long had you been trying to get pregnant when you saw that doctor?	☐ I saw the doctor before I started trying ☐ Up to 6 months ☐ 6 – 11 months ☐ 1 – 2 years ☐ Over 2 years
j)	What help did your doctor provide? *Tick all that apply* [If "referral" show k]	☐ Advice ☐ Testing, please specify_____ ☐ Referral to a fertility specialist ☐ Referral to general gynaecologist ☐ Other, please specify_____ ☐ No help was provided
k)	Did you get pregnant before seeing the	☐ Yes

	specialist?	☐	No [show l, m & n]
l)	How long did you wait to see a specialist after getting referred?	☐	Less than 1 month
		☐	1 – 6 months
		☐	Over 6 months
m)	Were any reasons found that explained why you were experiencing difficulties? *Tick all that apply*	☐	Ovulation problems
		☐	Blocked fallopian tubes
		☐	Endometriosis
		☐	My partner had sperm problems
		☐	I have unexplained infertility
		☐	Other, please specify _____
n)	Did you receive any of these treatments? *Tick all that apply* [If "IVF" show o & p, if "AI" show p, if options 1 – 5 show q]	☐	Drugs to improve ovulation
		☐	Artificial insemination
		☐	IVF (In vitro fertilization)
		☐	Surgery
		☐	Other, please specify _____
		☐	I got pregnant before starting any treatment
o)	Who provided the egg(s) for IVF?	☐	Myself
		☐	Anonymous donor
		☐	Known donor
p)	Who provided the sperm?	☐	My partner
		☐	Anonymous donor
		☐	Known donor
q)	Did this pregnancy occur as a direct result of your treatment?	☐	Yes
		☐	No
		☐	Not sure
r)	From the time you first started trying, how long did it take you to get pregnant? *Include time spent getting medical help*	☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years
s)	From the time you first started trying, how long did it take you to get pregnant?	☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years
t)	How long were you having regular intercourse (without using methods to avoid pregnancy) before you got pregnant?	☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years

[Page 6: Section 1, continued] [Show page if q3 not "yes"] [Show question 9]

9. Are you currently trying to get pregnant?

☐ Yes [show q10 & 10a] ☐ No

10. These questions are about your **current** experience of trying to get pregnant.

a)	Would you say that you are having difficulties	☐	Yes [show b & c]

	getting pregnant (or do you need medical help to get pregnant)?	☐	No [show m]
b)	Have you seen a GP, family planning or other non-specialist doctor about these difficulties?	☐ ☐	Yes [show e, f & l] No [show d]
c)	Have you seen a non-medical health provider about your difficulties? E.g. naturopath, homeopath, acupuncturist, traditional healer or educator	☐ ☐	Yes No
d)	Have you seen a fertility specialist or a gynaecologist?	☐ ☐	Yes [show e, h, i & l] No [show m]
e)	How long had you been trying to get pregnant when you saw that doctor?	☐ ☐ ☐ ☐ ☐	I saw the doctor before I started trying Up to 6 months 6 – 11 months 1 – 2 years Over 2 years
f)	What help did your doctor provide? *Tick all that apply* [If "referral" show g]	☐ ☐ ☐ ☐ ☐ ☐	Advice Testing, please specify_____ Referral to a fertility specialist Referral to general gynaecologist Other, please specify_____ No help was provided
g)	How long did you wait to see a specialist after getting referred? [If options 1 – 3 show h & i]	☐ ☐ ☐ ☐	Less than 1 month 1 – 6 months Over 6 months Not applicable, I have not seen the specialist yet
h)	Were any reasons found that explained why you were experiencing difficulties? *Tick all that apply*	☐ ☐ ☐ ☐ ☐ ☐	Ovulation problems Blocked fallopian tubes Endometriosis My partner had sperm problems I have unexplained infertility Other, please specify _____
i)	Did you receive any of these treatments? *Tick all that apply* [If "IVF" show j & k, if "AI" show k]	☐ ☐ ☐ ☐ ☐ ☐	Drugs to improve ovulation Artificial insemination IVF (In vitro fertilization) Surgery Other, please specify _____ Not applicable, I have recently seen the specialist
j)	Who provided the egg(s) for IVF?	☐ ☐ ☐	Myself Anonymous donor A known donor
k)	Who provided the sperm?	☐ ☐ ☐	My partner Anonymous donor A known donor

l)	From the time you first started, how long have you been trying to get pregnant? *Include time spent getting medical help*	☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years
m)	From the time you first started, how long have you been trying to get pregnant?	☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years

[Page 7: Section 1, continued] [Show questions 11 & 13]

[If q2="yes": "Some women may have tried in the past to get pregnant, **without a pregnancy occurring**. This fertility problem can occur even for women who have been pregnant. Therefore we now would like to ask questions that may seem repetitive."]

11. Have you ever had regular intercourse with a male partner for 12 months or more, without using any methods to avoid pregnancy, without a pregnancy occurring?
    ☐ Yes [show q12] ☐ No

12. How old were you when this first happened? _____ years

13. Have you ever tried unsuccessfully to get pregnant?
    ☐ Yes [show q14] ☐ No

14. How old were you when this first happened? _____ years

[Page 8: Section 1, continued] [Show page if q13="yes"] [Show questions 15, 15a & b]

15. These questions are about the **time(s) in the past when you tried unsuccessfully to get pregnant.**

a)	Did you ever see a GP, family planning, or other non-specialist doctor about difficulties getting pregnant?	☐	Yes [show d, e & k]
		☐	No [show c]
b)	Did you ever see a non-medical health provider about difficulties getting pregnant? E.g. naturopath, homeopath, acupuncturist, traditional healer or educator	☐	Yes
		☐	No
c)	Did you ever see a fertility specialist or a gynaecologist for help getting pregnant?	☐	Yes [show d, g, h & k]
		☐	No [show l]
d)	Initially, how long had you been trying to get pregnant when you saw that doctor?	☐	I saw the doctor before I started trying
		☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years
e)	What help did your doctor provide? *Tick all that apply* [If "referral" show f, g & h]	☐	Advice
		☐	Testing, please specify_____
		☐	Referral to a fertility specialist

		☐	Referral to general gynaecologist
		☐	Other, please specify_____
		☐	No help was provided
f)	How long did you wait to see a specialist after getting referred?	☐	Less than 1 month
		☐	1 – 6 months
		☐	Over 6 months
		☐	Not applicable, I have only recently been referred
g)	Were any reasons found that explained why you were experiencing difficulties? *Tick all that apply*	☐	Ovulation problems
		☐	Blocked fallopian tubes
		☐	Endometriosis
		☐	My partner had sperm problems
		☐	I have unexplained infertility
		☐	Other, please specify _____
h)	Did you receive any of these treatments? *Tick all that apply* [If "IVF" show i & j, If "AI" show j]	☐	Drugs to improve ovulation
		☐	Artificial insemination
		☐	IVF (In vitro fertilization)
		☐	Surgery
		☐	Other, please specify _____
i)	Who provided the egg(s) for IVF?	☐	Myself
		☐	Anonymous donor
		☐	Known donor
j)	Who provided the sperm?	☐	My partner
		☐	Anonymous donor
		☐	Known donor
k)	Overall, what was the longest period you tried to get pregnant (without it occurring)? *Include time spent getting medical help*	☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years
l)	Overall, what was the longest period you tried to get pregnant (without it occurring)?	☐	Up to 6 months
		☐	6 – 11 months
		☐	1 – 2 years
		☐	Over 2 years

[Page 9: Section 2, fertility expectations] [Show page if q4>0 or q9 not "yes"] [Show questions 16 if q4>0 & 17 if q9 not "yes"]

16. Just to confirm (and as some women may have had twins, triplets etc), how many children have you given birth to (excluding stillbirths)?

☐ None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 or more, please specify

17. Do you plan to get pregnant in the future?

☐ Yes, definitely ☐ Yes, possibly ☐ Unsure ☐ Probably not ☐ Definitely not

☐ Not applicable, I am not able to get pregnant in the future

☐ Not applicable/other, please specify _____

[If options 1 – 2 show q18]

18. If, in the future, you felt you were having difficulties getting pregnant, would you seek medical advice?

☐ Yes [show q19] ☐ No

19. How long would you wait before seeking medical help medical help if you were trying to get pregnant without success?

☐ Up to 6 months ☐ 6 – 11 months ☐ 1 – 2 years ☐ Over 2 years

[Page 10: Section 2, continued]

20. Do you wish you had had more children? [Show if q9 not "yes" & q3="no" & q17= options 4-6 & q16>0 & q1>39]

☐ No, not at all ☐ A little ☐ Somewhat ☐ Yes, very much

21. Do you wish you had had any children? [Show if (q9 not "yes" & q3 not "yes" & q17= options 4-6 & q2="no") or (q9 not "yes" & q3 not "yes" & q17= options 4-6 & q16=0) & q1>39]

☐ No, not at all ☐ A little ☐ Somewhat ☐ Yes, very much

22. At what age would you like to have your first child? [Show if (q2="no" & q17= options 1-2) or (q16=0 & q17= options 1-2) & q1<40]

☐ 25 – 29 years ☐ 30 – 34 years ☐ 35 – 39 years ☐ 40 – 45 years ☐ 45 years or more

23. How important is it for you to have children sometime in the future? [Show if (q16=0 & q17= options 1-2) or (q16=0 & q9="yes") or (q2="no" & q17= options 1-2) or (q2="no" & q9="yes")]

☐ Not important ☐ Only a little important ☐ Moderately important ☐ Very important

24. How important is it for you to have more children sometime in the future? [Show if (q16>0 & q17= options 1-2) or (q16>0 & q9="yes")]

☐ Not important ☐ Only a little important ☐ Moderately important ☐ Very important

[Page 11: Section 3, health conditions and behaviours] [Show questions 25-27, 29/30 & 34-37]

We would now like to ask all women participating in this survey about conditions that may affect fertility.

25. Have you ever had any of the following procedures? *Tick all that apply*

☐ Chemotherapy
☐ Sterilisation (removing or tying your fallopian tubes)
☐ Any operation on your ovaries
☐ Appendicectomy (removal of your appendix)
☐ Hysterectomy (removal of your womb)
☐ Any other operation in the lower abdomen / pelvis, please specify_____
☐ None of the above

26. If you currently have a male partner, has he had a vasectomy?

☐ Yes ☐ Yes, but it has been reversed ☐ No ☐ Don't know ☐ Not applicable

27. Have you ever been diagnosed with any of the following? *Tick all that apply*

☐ Polycystic ovary syndrome
☐ Pelvic inflammatory disease
☐ A sexually transmitted infection
☐ None of the above
☐ Fibroids
☐ Endometriosis
☐ Other gynecological problem, please specify_____

28. Which sexually transmitted infection(s) were you diagnosed with? *Tick all that apply* [Show if STI selected above]

☐ Herpes
☐ Warts
☐ Other, please specify_____
☐ Chlamydia
☐ Gonorrhoea

29. Have you ever been diagnosed with a fertility problem? [Show if q2 & q9 & q13 not "yes"]

☐ Yes [show q31, 32 & 33] ☐ No

30. Have you ever been diagnosed with a fertility problem that you have not already had the chance to mention in this questionnaire? [Show if q2 or q9 or q13 = "yes"]

☐ Yes [show q31, 32 & 33] ☐ No

31. How old were you when you were diagnosed with this? _____ years

32. Did any of the following cause your fertility problem? *Tick all that apply*

☐ Ovulation problems
☐ Endometriosis
☐ I don't know the cause
☐ Blocked fallopian tubes
☐ My partner had sperm problems
☐ Other, please specify_____

33. Did you receive any treatment?

☐ Yes, please specify_____ ☐ No

34. Do you have any long-term health problems?

☐ Yes, please specify_____ ☐ No

35. What is your height? *You can give your answer either in centimetres or in feet and inches.*

In centimetres:
_____ [100-220 valid]
Or, in feet: and inches:
_____ [4-7 valid] _____ [0-12 valid]

36. What is your weight? *You can give your answer either in kilograms or in stones and pounds.*

In kilograms:
_____ [35-160 valid]
Or, in stones: and pounds:
_____ [4-20 valid] _____ [0-14 valid]

37. Do you smoke cigarettes regularly (that is, one or more a day)?

☐ Yes ☐ No [show q 38]

38. Have you ever been a regular smoker of one or more cigarettes a day?

☐ Yes ☐ No

[Page 12: Section 4, fertility knowledge] [Show all questions]

This section will help us get an understanding of women's awareness of fertility and infertility.

39. Day 1 of the menstrual cycle is the first day of a woman's period and on average a menstrual cycle is 28 days long. If a woman ovulates (produces an egg) on day 14 of her menstrual cycle, on which days is it possible to get pregnant?
Please select the one answer you think is correct.

☐ Days 7 to 21 ☐ Days 14 to 17

☐ Days 11 to 14* ☐ Days 11 to 17

40. Have you ever used any of the following methods to time when you ovulate? *Tick all that apply*

☐ The calendar method ☐ Basal-temperature charting

☐ Ovulation test kits ☐ Other, please specify_____

☐ I have not tried to monitor when I ovulate

41. What was your reason for monitoring ovulation? *Tick all that apply* [Show if options 1 – 4 selected above]

☐ I was trying to get pregnant ☐ I was trying to avoid pregnancy

☐ I wanted to learn about my cycle ☐ Other, please specify_____

42. Where did you learn about how to monitor your cycle? *Tick all that apply* [Show if options 1 – 4 selected above]

☐ A GP, family planning or other non-specialist doctor ☐ A fertility specialist or gynaecologist

☐ A non-medical health provider (e.g. naturopath, homeopath, acupuncturist, traditional healer or educator) ☐ Friends and / or family

☐ The internet ☐ Other, please specify_____

For the following four questions, please select the one answer you think is correct.

43. At which age does women's fertility start to decline? Approximately…

☐ 25 years ☐ 30 years

☐ 35 years ☐ 40 years

44. For women aged 30 – 35 years having regular intercourse without using methods to avoid pregnancy, what is the average chance of conception each month?

☐ 5 – 10% ☐ 15 – 25%

☐ 35 – 50% ☐ 55 – 70%

45. For women aged 30 – 35 years having IVF (In vitro fertilisation), what is the average chance of conception resulting in a live birth after one treatment?
IVF is the fertilisation of an egg by sperm outside the body (resulting in a "test-tube" baby)

☐ 5 – 10%
☐ 15 – 25%
☐ 35 – 50%
☐ 55 – 70%

46. What percentage of all couples attempting to have children experience problems getting pregnant (infertility)?

☐ 0 – 10%
☐ 15 – 25%
☐ 30 – 40%
☐ 45 – 55%

There is not enough public funding available for IVF treatment for all infertile women in New Zealand, as it costs about $10,000 per treatment. The chance of successful treatment is significantly reduced if a woman is over 40 years old, under or over-weight, or a smoker.

47. Which of the following do you think should **restrict** eligibility for free treatment?

☐ Being aged less than 25 years
☐ Being aged more than 40 years
☐ Smoking
☐ Being substantially overweight (Body Mass Index of more than 32)
☐ Not in a stable relationship
☐ Not in a heterosexual relationship
☐ Already having at least 1 child with current partner
☐ Already having at least 1 child, but no children with current partner
☐ I do not think any of these should be criteria

[Page 13: Section 5, background information] [Show questions 48-51 & 55]

This is the last page of the questionnaire. We would just like to ask a few more questions to gather some background information.

48. Which ethnic group do you belong to? *Tick all that apply to you*

☐ New Zealand European
☐ Māori
☐ Samoan
☐ Cook Island Maori
☐ Tongan
☐ Niuean
☐ Chinese
☐ Indian
☐ Other such as Dutch, Japanese, Tokelauan.
Please specify:_____

49. Are you descended from a Māori (that is, did you have a Māori birth parent, grandparent or great-grandparent, etc)?

☐ Yes ☐ No ☐ Don't know

50. What is your highest completed qualification?

☐ Left school without a qualification
☐ School certificate/NCEA level 1
☐ Sixth form certificate/NZ university entrance/NCEA level 2
☐ NZ university bursary/scholarship/ NCEA level 3
☐ Trade certificate/vocational training
☐ Polytechnic degree
☐ University undergraduate degree
☐ University postgraduate degree
☐ Other, please specify_____

51. What is your current relationship status?

- ☐ Married or living with a male partner
- ☐ Male partner but not living together
- ☐ Civil union or living with a female partner
- ☐ Female partner but not living together
- ☐ Not in a relationship

[If options 1 – 4 show q52 – 54]

52. How long have you been in this relationship?

- ☐ Up to 1 year
- ☐ 1 – 2 years
- ☐ 3 – 4 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years
- ☐ 20 or more years

53. Which ethnic group does your partner belong to? *Tick all that apply*

- ☐ New Zealand European
- ☐ Tongan
- ☐ Māori
- ☐ Niuean
- ☐ Samoan
- ☐ Chinese
- ☐ Cook Island Maori
- ☐ Indian
- ☐ Other such as Dutch, Japanese, Tokelauan.
  Please specify:_____
- ☐ Don't know

54. Is your partner descended from a Māori (that is, did your partner have a Māori birth parent, grandparent or great-grandparent, etc)?

- ☐ Yes
- ☐ No
- ☐ Don't know

55. What is your annual household income before tax?

- ☐ $20,000 or Less
- ☐ $50,001 - $70,000
- ☐ $20,001 - $30,000
- ☐ $70,001 - $100,000
- ☐ $30,001 - $50,000
- ☐ $100,001 or More

[Page 14: contact information][Show questions 56 & 57]

56. Do you want to enter the draw to win a $200 grocery voucher?

- ☐ Yes [show q58]
- ☐ No

57. Do you wish to be e-mailed a summary of the study results?

- ☐ Yes [show q58]
- ☐ No

58. Please provide your first name and an e-mail address (this will not be linked to your questionnaire responses) so we can contact you.

a) Name: _____

b) E-mail address: _____

[Page 15: submit]

Thank you for completing this questionnaire.
You can close this window now.

APPENDIX C: PAPER-BASED QUESTIONNAIRE

Merge field [ID]

Fertility Experiences and Expectations Survey: Reply Form

If you prefer not to complete the survey online, we would be grateful if you would indicate whether you can participate by (a) telephone interview, or (b) completing the short questionnaire below. Or please tick the third box to let us know that you do not want to take part.

☐ **Telephone Interview:** Please provide your number and we will contact you to arrange a suitable time. We are happy to interview in the evenings or weekends.

Number: _____

☐ **Short questionnaire:** Please answer these questions

1. Have you ever been pregnant? ☐ Yes ☐ No
   If no: *Skip questions 2 - 5*
   If yes: How old were you the first time you got pregnant? _____

2. How many times have you been pregnant? _____
   Include current pregnancy (if applicable)

3. Did you ever spend 12 months or more trying to get pregnant for any one of these pregnancies? ☐ Yes ☐ No
   If yes: How old were you when this first happened? _____

4. Did you ever receive medical help to get pregnant for any of these pregnancies? ☐ Yes ☐ No
   If yes: How old were you when this first happened? _____

5. How many children have you given birth to (live births)? _____

6. Have you ever tried to get pregnant without a pregnancy occurring (yet)? ☐ Yes ☐ No
   If yes: How old were you when this first happened? _____
   Did you ever receive medical help for this? ☐ Yes ☐ No
   Did you spend 12 months or more trying (so far)? ☐ Yes ☐ No

7. Do you plan to get pregnant in the future?
   ☐ Yes, definitely
   ☐ Yes, possibly
   ☐ Unsure
   ☐ Probably not
   ☐ Definitely not
   ☐ Not applicable

8. Which ethnic group(s) do you belong to? Tick all that apply to you
   ☐ NZ European
   ☐ Māori
   ☐ Other, please specify _____

☐ **I do not want to take part or be contacted again**

Please return the completed form in the reply-paid envelope. Thank you.

APPENDIX D: STUDY INVITATION LETTER

[DATE]

Dear [Title] [Surname],

Fertility experiences and expectations of Otago and Southland women

The Dunedin School of Medicine and the Otago Fertility Service invite you to complete an online questionnaire on fertility. Your participation will help us to understand local fertility and service issues. This is a topic of growing concern with changes in fertility patterns in the last few decades. Therefore the survey also has the support of Natural Fertility New Zealand, a charitable organisation providing fertility education and advice.

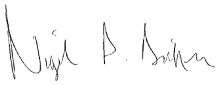
In appreciation of your time, upon completing the survey you can enter a draw to **win one of three $200 grocery vouchers** and/or choose to receive a summary of the research results. A teabag is enclosed, so when you get a moment you can sit down with a cup of tea and complete the short online questionnaire. A few points to note:

- **You can complete the questionnaire yourself online or a telephone interview can be arranged**
- To complete online please type or copy the following address into your internet browser address bar: **http://fertility.otago.ac.nz/s3/survey**, your password is: **[ID]**
  Do not use an Internet search engine such as Google, this a private site and is not searchable
- **Your response is important to us, even if you have never tried to get pregnant and/or do not intend to in the future**
- The questionnaire is designed to capture the various circumstances in which women may experience fertility (or infertility), including women in same-sex relationships and women without partners
- You can skip any question that you that feel is inappropriate for your situation

If you would prefer to participate by telephone interview or if you prefer not to be contacted again about this survey, then please tick the appropriate box on the enclosed slip and return it in the post-paid envelope. Or you can contact Antoinette Righarts (researcher at the Dunedin School of Medicine) on (03) 477 0454 or antoinette.righarts@otago.ac.nz.

You were randomly selected from the electoral roll to take part in this survey. The survey is confidential and your personal information will not be connected to your responses. The Southern Region Ethics Committee has approved this survey. Thank you for taking the time to complete the questionnaire or return the reply slip to us.

Yours Sincerely,



Assoc. Prof Nigel Dickson
Dunedin School of Medicine

Assoc. Prof Wayne Gillett
Otago Fertility Service

APPENDIX E: TEMPLATE FOR E-MAIL FOLLOW UP OF NON-RESPONDERS

From: **Antoinette Righarts** antoinette.righarts@otago.ac.nz
Subject: Fertility Study
Date: 13 August 2014 10:13 am
To:

Dear Ms. [SURNAME],

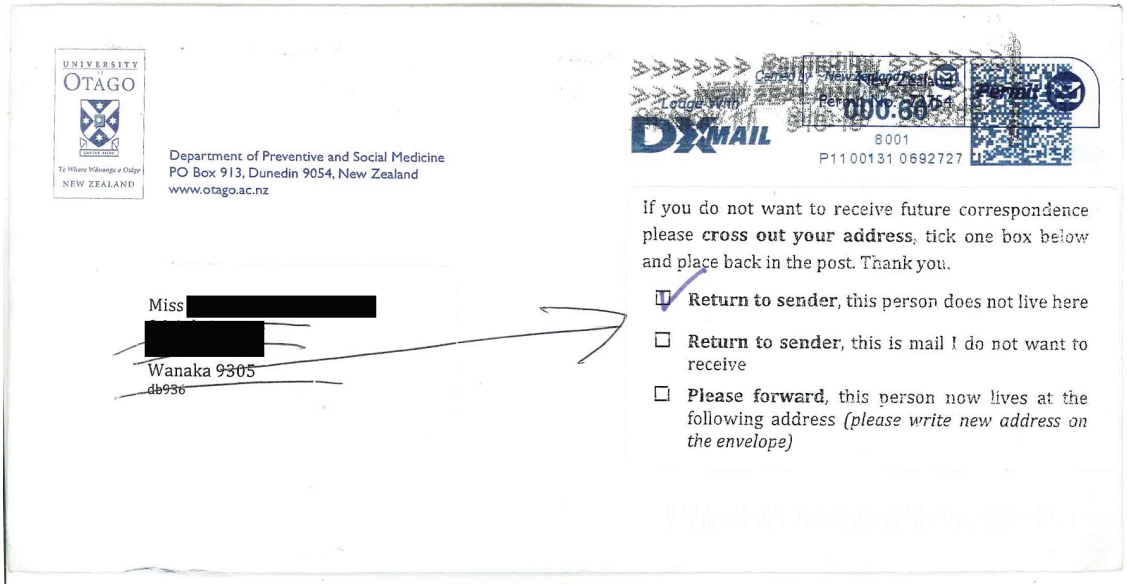
As per our telephone conversation today I have pasted the link and password for the fertility study at the end of this e-mail. We would very much appreciate your participation if you can find the time - it takes about 10-15 minutes and the survey site will be open up to and including **Sunday 11 December**. If you want any further information (or if this link doesn't work on your computer) please contact me.

Link: http://fertility.otago.ac.nz/s3/survey
Password: [PASSWORD]

Kind regards,
Antoinette

Antoinette Righarts
Dunedin School of Medicine
Tel: +64 (0) 3 477 0454
antoinette.righarts@otago.ac.nz

APPENDIX F: EXAMPLE OF MONITORING THE REASON FOR NON-RESPONSE THOUGH RETURNED MAIL



UNIVERSITY OF OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Department of Preventive and Social Medicine
PO Box 913, Dunedin 9054, New Zealand
www.otago.ac.nz

Lodged with DX MAIL

8001
P1100131 0692727

Miss [redacted]
[redacted]
Wanaka 9305
db93o

If you do not want to receive future correspondence please **cross out your address**, tick one box below and place back in the post. Thank you.

- ☑ **Return to sender**, this person does not live here
- ☐ **Return to sender**, this is mail I do not want to receive
- ☐ **Please forward**, this person now lives at the following address *(please write new address on the envelope)*

APPENDIX G: RECODING OF SERVICE VARIABLES BASED ON SPECIFIED 'OTHER' RESPONSE

Questions and specified responses* to 'other' categories	Adjustments
What help did your doctor provide? *Other, please specify*	
'ovulation recording', 'plan to cope the pain and hyperemesis in pregnancy, and the extreme pelvic dysfunction that resulted in loss of mobility in the previous pregnancy'	'Other' recoded to 'No', 'Advice' recoded to 'Yes'.
'sperm movement', 'sperm test', 'MRI scan', 'ultrasound of uteris etc', 'laporoscopy'	'Other' recoded to 'No', 'Testing' recoded to 'Yes'.
'referral for gynaecological laparoscopic surgery', 'referal to [name of fertility specialist removed] where we paid privately for vasectomy reversal november 16th 2010', 'tubes etc [name of fertility specialist removed]'	'Other' recoded to 'No', 'Referral' recoded to 'Yes'.
'medically qualified- didn't need advice etc'	'Other' recoded to 'No'.
'severe pain issues around midcycle preventing natural means of getting pregnant, pain control over cycle', 'medication', 'clomiphene', 'medication – metformin', 'steroids', 'clomapene because no periods', 'slushish sperm', 'fertility drugs'	No adjustments needed.
Were any reasons found that explained why you were experiencing difficulties? *Other, please specify*	
'premature ovarian failure', 'polycistic ovaries' (twice), 'polycitic ovaries', 'polycitic ovaries', 'PCOS', 'polycystic', 'pco', 'Polycystic Ovarian Syndrome', 'polycystic'.	'Other' recoded to 'No', 'Ovulation disorder' recoded to 'Yes'.
'tube problems' (twice), 'only one tube', 'I had an operation as i had. had problems with my stomach. They removed both fallopian tubes as they were damaged.', 'polyps in fallopian tubes', 'just to check, needed tubal reversal (were just tied, not snipped)', 'both tubes removed from due ectopics', 'see last, no tubes'.	'Other' recoded to 'No', 'Tubal disorder' recoded to 'Yes'.
'vasectomy' (four times), 'My first husband', 'husband had vescimty', 'Vasectomy' (twice).	'Other' recoded to 'No', 'Male factor' recoded to 'Yes'.
'no problems at all were found..we both had fertility tests done'.	'Other' recoded to 'No', 'Unknown cause' recoded to 'Yes'.

Questions and specified responses* to 'other' categories	Adjustments
'We did get pregnant but it took longer than I unrealistically expected. We concieved before we saw the specialist.', 'I got pregnant before seeing the specialist'.	'Other' and all other diagnosis categories recoded to 'missing' (as not eligible).
'I was never able to get pregnant naturally', 'Endo was suspected. Followed by laparoscopy. (No Endo)', 'we had no problems at all were just trying to hard'.	'Other 'recoded to 'No'.
'half a uterus, not sure what it is called, I was born with, then a pelvic absess to cause damage to one tube.', 'uterine uterus, and after surgery 2 tubes on the one side'.	'Tubal disorder' recoded to 'Yes'.
'being over weight', 'polyps' (twice), 'Resulting from infection/appendicitus', 'microprolactinoma', 'polyps, heavy bleeding', 'septim', 'vagismus', 'I have a microprolactinoma', 'Hostile Mucus', (twice) 'a large septim deviding my uteris', 'pitutary adenoma', 'stress about pregnancy', 'Pain and extreme sensitivity to own hormonal changes', 'cyst & scar tissue', ', scarred', 'Large uterine fibroids', 'severe pain and extreme Pelvic dysfunction effecting mobility and other illness', 'sperm donor because we have a genetic imcompatibility resulting in the death of our first child', 'Scarring'.	No adjustments needed.
Did you receive any of these treatments? *Other, please specify*	
'drugs', 'metformin', 'drugs to ovulate/reduce prolactin levels', 'metformin drugs'	'Other' recoded to 'No', 'Drugs' recoded to 'Yes'.
'doner inseminations', 'IUI'	'Other' recoded to 'No', 'AI/IUI' recoded to 'Yes'.
'icsi', 'ICSI' (three times)	Other' recoded to 'No', 'IVF' recoded to 'Yes'.
'D n C', 'laproscopy, d&c', 'surgery to unblock tubes', 'tubal ligation and flush, scar tissue removed, lost tube', 'tubal reversal', 'laproscopy, hcg'	'Other' recoded to 'No', 'Surgery' recoded to 'Yes'.
'waiting still for donor (2+ years)', 'going to see her privately in September' , 'relationship ended', 'living in southland so didn't access treatment'	'Other' recoded to 'No', 'No treatment received' recoded to 'Yes'.
'With my first husband', 'I was offed IVF but never did it', 'pain sevice involvement, hospitalisation, close monitoring of baby and self'	'Other' recoded to 'No'

* *All responses are reported verbatim in quotation marks.*

APPENDIX H: CPAC SCORING TOOL

Step 1. From history and assessment complete all 6 scores for the **DIAGNOSTIC SCORE (DS)**.

1) Ovulation defects		**(2) Semen defects**		**(3) Tubal/peritoneal factor**	
• Amenorrhoea – any cause	**6**	• Azoospermia – any cause • Density < 1 million motile sperm/ml • Mar test > 90% • Severe ejaculatory dysfunction	**6**	• Tubal occlusion best side / missing tubes or • Severe tubal or ovarian adhesions best side or • Partial distal occlusion with moderate ovarian adhesions best side or • Unsuccessful tubal surgery after 12 months	**6**
• Oligomenorrhoea from any cause	**3**	• 1<5 million motile sperm / ml • Mar test 30-90% • Repeat negative PCT	**3**	• Moderate adhesions best side or • Unsuccessful tubal surgery after 12 months	**3**
• Anovulation with normal menstrual cycle	**2**	• 5<10 million motile sperm / ml	**2**	• Tubal polyps / mild adhesions best side • Occluded tube one side	**2**
• Intermittent anovular cycle	**1**	• Any other sperm defect with normal postcoital test	**1**	• Minimal adhesions best side	**1**
• Normal ovulation	**0**	• Normal semen analysis	**0**	• Normal or not assessed	**0**
Score 1		**Score 2**		**Score 3**	

(4) Endometriosis		**(5) Other factors**		**(6) Unexplained infertility**	
• Stage IV ASRM classification	**6**	• Severe (e.g. fibroids/cervical pathology/psycho-sexual)	**6**	• Unexplained ≥ 5 years	**6**
• Stage III ASRM classification	**3**	• Moderate	**3**	• Unexplained ≥ 4 < 5 years	**3**
• Stage II ASRM classification	**2**	• Mild	**2**	• Unexplained ≥ 3 < 4 years	**2**
• Stage I ASRM classification	**1**	• Minimal	**1**	• Unexplained < 3 years	**1**
• No endometriosis or not assessed	**0**	• None	**0**		
Score 4		**Score 5**		**Score 6**	

Step 2. Add scores 1,2,3,4,5,6 = Score DS = now ☐ **1 year** ☐

Step 3. Calculate Priority Scores

	Criteria	**Categories**	**Points**	**Points now**	**Points 1 year**
O1	Diagnosis	DS≥6	**10**	☐	☐
		DS=3 <6	**7**		
		DS=2	**4**		
		DS=1	**2**		
O2	Woman's age	≤ 39 years	**10**	☐	☐
		40-41 years	**5**		
		42 +	**1**		
S1	Duration of infertility	≥5 years	**50**	☐	☐
		3<5 years	**40**		
		1<3 years	**20**		
		<1 year	**10**		
S2	Number of children	None	**30**	☐	
		1 current relationship	**10**		
		>1 current relationship	**5**		
		≥1 previous relationship	**8**		
S3	Sterilisation reference range	Neither partner sterilised	**20**	☐	
		Death of child	**20**		
		One partner sterilised	**10**		

Objective Score (OS) = (O1 x O2)/100

OS now	**OS 1 year**

Social Score (SS) = S1 + S2 + S3

SS now	**SS 1 year**

PS now	**PS 1 yr**

Priority Score (PS) = OS x SS

APPENDIX I: SUMMARY OF HYPOTHESISED RELATIONSHIPS PRESENTED IN FIGURE 4.1

Arrow	Summary of proposed relationship	P-value*
1	Lower SES associated with higher withdrawal (hypothesised due to the higher rates of mobility, loss to follow up and relationship break down).	<0.001
2	Lower SES associated with higher parity.	0.005
3	Lower SES associated with higher smoking.	<0.001
4	Lower SES associated with higher BMI.	0.001
5	Lower SES associated with higher levels of tubal/peritoneal disorder (hypothesised based on higher risk of reproductive tract infections).	0.006
6	Lower SES associated with lower levels of treatment (hypothesised based on likely reduced income versus high cost if not eligible for public funding of treatment).	0.002
7	Māori ethnicity associated with lower SES than European.	<0.001
8	Māori ethnicity associated with higher parity than European.	0.001
9	Māori ethnicity associated with higher smoking than European.	<0.001
10	Māori ethnicity associated with higher BMI than European.	0.063
11	Māori ethnicity associated with (a) higher levels of TFI and (b) lower levels of endometriosis than European.	a: 0.006 b: 0.027
12	Māori ethnicity associated with younger age than New Zealand European.	0.171
13	Smoking associated with reduced treatment due to funding access (being a smoker disqualifies patients from public funding).	<0.001
14	Smoking associated with reduced resolution of infertility.	0.009
15	Smoking associated with lower BMI.	0.654
16	Higher BMI associated with increased 'other treatment' (such as weight reduction advice) and non-treatment (due to not meeting BMI restrictions for funding of treatment), increased OI and decreased IVF.	<0.001
17	Higher BMI associated with reduced resolution of infertility (due to increased risk of PCOS).	<0.001
18	Higher BMI associated with increased ovulatory disorder diagnoses (due to increased risk of PCOS).	<0.001

Arrow	Summary of proposed relationship	P-value
19	Increased age associated with higher parity.	0.001
20	Increased age associated with higher BMI.	0.304
21	Increased age associated with reduced funding access (being over 40 years old disqualifies patients from public funding).	<0.001
22	Younger age associated with higher withdrawal (hypothesised as young people are more mobile and have more fluid relationships).	0.486
23	Increased age associated with reduced resolution of infertility (due to decrease in fecundability with age).	<0.001
24	Higher parity associated with reduced funding access (funding is more restricted for those who already have a child).	<0.001
25	Higher parity associated with increased withdrawal (hypothesised due to those with children being less motivated to commit to an infertility programme).	0.732
26	Longer duration of care associated with decreasing resolution of infertility	<0.001
27	Longer duration of care associated with increased treatment/more advanced treatment	<0.001
28	Higher diagnostic score associated with increasing duration of care	<0.001
29	Higher diagnostic score associated with increased funding access (as the overall diagnostic score is incorporated into funding access [CPAC] scores).	<0.001
30	Higher diagnostic score associated with reduced levels of other and no treatment, and increased IVF.	<0.001
31	Higher diagnostic score associated with reduced resolution of infertility.	<0.001
32	Access to public funding associated with higher levels of ARTs (especially IVF) and lower other and no treatment.	<0.001
33	ARTs associated with decreased withdrawal, other and no treatment associated with increased withdrawal (ARTs, IVF especially, require a high level of commitment, whereas referral to dieticians and weight loss advice would likely lead to high levels of withdrawal, especially amongst those who were not successful with reducing their weight).	<0.001
34	Receiving treatment associated with increased resolution of infertility compared with other and no treatment.	<0.001

Arrow	Summary of proposed relationship	P-value
35	Single and lesbian relationship types associated with decreased diagnostic severity compared with heterosexual couples (as single and lesbian women are accessing the clinic due to social rather than physical causes of infertility).	<0.001
36	Single and lesbian relationship types associated with increased IUI/DI and decreased ovulation induction, other and no treatment compared with heterosexual couples.	<0.001
37	Single and lesbian relationship types associated with decreased duration of infertility compared with heterosexual couples (as under most circumstances they have not been having regular coitus, so have not been 'trying' to become pregnant).	<0.001
38	Single and lesbian relationship types associated with reduced resolution of infertility (as under most circumstances they cannot have a spontaneous pregnancy).	<0.001
39	Withdrawal associated with decreased duration of care	<0.001
40	By definition, those who withdrew before conclusion of their infertility programme could not have resolved their infertility before withdrawal (as resolving infertility would conclude the episode of treatment/care).	<0.001
41	Increased duration of infertility associated with increased funding (as duration of infertility is incorporated into funding access (CPAC) scores).	<0.001
42	Increased duration of infertility associated with decreased withdrawal (e.g. if those who have had infertility for longer are more committed to receiving help).	0.492

* *P-values derived from Pearson's chi-squared tests comparing these variables in the OFS dataset (refer to Section 4.3.7).*

APPENDIX J: METHODS FOR COX'S PROPORTIONAL HAZARDS MODELLING AND COMPETING RISK ASSESSMENT FOR RESOLUTION OF INFERTILITY

Time to resolution of infertility was measured by deducting the date of the patient's final follow up from the date of their first referral, and dividing this number by 365.25 to give a denominator of person years of observation (pys). For those patients who resolved their infertility, the date of their final follow up corresponded with the date of the diagnosis of pregnancy (which was usually of between five and eight weeks of gestation). This resulted in 73 women with a follow up time of zero, as they physically attended just one appointment, these women were given a follow up time 0.01 years.

Survival techniques were used to estimate the time to pregnancy ending in live birth amongst these patients. The number of events, total person years at risk and the rates of events per 100 person-years were calculated for each level of all variables hypothesised to be either directly or indirectly related to resolved infertility (refer to Figure 4.1 on page 167). Unfortunately, predominant treatment could not be included in the model due to the complexity of multiple treatment types and varying treatment exposure times. Withdrawing due to a relationship separation was identified as a competing risk, as this event prevents the outcome (resolution of infertility) from occurring (unlike censoring which just prevents the outcome from being observed). Therefore, sub-hazard ratios (SHR) were calculated for each of predictor variable using competing risk regression, employing the method outlined by Fine and Gray (1999).

A multivariate model was built using the criteria set out previously for Poisson regression models. The model assumption of proportional hazards was checked by comparing plotted hazard functions to detect any significant time varying patterns in the covariates. As with the Poisson models, the final model's internal validity was formally quantified by using the bootstrapping method for regression. Each categorical parameter in the model was also checked for overall significance using Wald tests. Hazard ratios (HR) were then calculated for each of the predictor

variables that were included in the final competing risk multivariate model using Cox's proportional hazards regression (data not shown). The Cox's proportional hazards regression HRs and the competing risk regression SHRs were compared with determine whether there were any strong effects due to the competing risk. The rates, unadjusted and adjusted SHRs, as well as the 95% CIs and Wald test p-values were reported.

Following competing risk regression, the cumulative incidence functions were graphed for each of the significant predictor variables. These graphs were restricted to five years of survival time, after which there was significant censoring and very few events.

APPENDIX K: CRUDE AND ADJUSTED SUB-HAZARD RATIOS FOR RESOLVING INFERTILITY BY DEMOGRAPHIC FACTORS, OTHER RISK DETERMINANTS, DURATION OF INFERTILITY, DIAGNOSES AND FUNDING ELIGIBILITY

		Number live births	Time at risk (pys)	Rate (per 100 pys)	Unadjusted*			Adjusted†		
					SHR	(95 CI%)	P-value	SHR	(95 CI%)	P-value
Demographic factors										
Parity	0	533	1,740	30.6	Reference					
	≥1	230	560	41.1	1.26	(1.07–1.47)	0.004	1.37	(1.16–1.62)	<0.001
Relationship type	Heterosexual	750	2,218	33.8	Reference					
	Same-sex/no relationship	13	82	15.9	0.46	(0.28–0.77)	0.003	0.37	(0.22–0.63)	<0.001
Age group (years)	<30	263	670	39.2	1.07	(0.91–1.26)		1.15	(0.97–1.37)	
	30–34	310	884	34.9	Reference					
	35–39	161	611	26.3	0.72	(0.59–0.87)		0.73	(0.59–0.89)	
	≥40	29	130	22.3	0.58	(0.40–0.86)	<0.001	0.53	(0.35–0.81)	<0.001
Ethnic group	European	693	2,054	33.7	Reference					
	Māori	35	108	32.4	0.92	(0.63–1.35)				
	Other	35	138	25.4	0.77	(0.56–1.06)	0.249			
Deprivation	Low (deciles 1–3)	352	946	37.9	Reference					
	Medium (deciles 4–7)	310	985	32.2	0.87	(0.75–1.01)		0.87	(0.74–1.02)	
	High (deciles 8–10)	98	358	27.7	0.70	(0.56–0.86)	0.003	0.74	(0.59–0.92)	0.019

Appendix K *continued*		Number live births	Time at risk (pys)	Rate (per 100 pys)	Unadjusted*			Adjusted†		
					SHR	(95 CI%)	P-value	SHR	(95 CI%)	P-value
Other risk determinants										
Current smoker	No	635	1,887	33.7	Reference					
	Yes	128	413	31.0	0.87	(0.72–1.05)	0.156			
BMI category, range (kg/m^2)	Underweight, <18.5	11	48	23.2	0.67	(0.36–1.25)				
	Normal, 18.5–24.9	443	1,292	34.3	Reference					
	Overweight, 25.0–29.9	140	412	34.0	1.02	(0.85–1.23)				
	Obese class I, 30.0–34.9	96	248	38.7	1.11	(0.90–1.38)				
	Obese class II, 35.0–39.9	25	115	21.8	0.69	(0.45–1.05)				
	Obese class III, ≥40.0	14	97	14.4	0.45	(0.26–0.77)	0.013			
Diagnostic variables										
Duration of infertility (years)	<2	363	951	38.2	Reference					
	2–4	267	828	32.2	0.84	(0.72–0.98)				
	>4	94	411	22.9	0.61	(0.48–0.77)	<0.001			
Severe tubal/peritoneal disorder	No	683	1,917	35.6	Reference					
	Yes	80	383	20.9	0.59	(0.48–0.73)	<0.001			
Severe endometriosis	No	755	2,205	34.2	Reference					
	Yes	8	95	8.5	0.27	(0.13–0.53)	<0.001			

Severe ovulation disorder	No	726	2,165	33.5	Reference					
	Yes	37	134	27.5	0.87	(0.61–1.23)	0.437			
Severe semen disorder	No	620	1,757	35.3	Reference					
	Yes	143	543	26.3	0.73	(0.62–0.87)	<0.001			
Severe other infertility	No	747	2,241	33.3	Reference					
	Yes	16	59	27.1	0.78	(0.49–1.25)	0.300			
Severe unexplained infertility	No	687	1,949	35.2	Reference					
	Yes	76	351	21.7	0.64	(0.50–0.82)	<0.001			
Number of severe diagnoses	0	487	1,173	41.5	Reference					
	1	268	1,045	25.6	0.62	(0.54–0.72)				
	≥2	8	82	9.8	0.23	(0.12–0.45)	<0.001			
Number of diagnoses	<2	557	1,537	36.2	Reference					
	≥2	206	763	27.0	0.77	(0.66–0.89)	<0.001			
Combined diagnostic score	Minimal	109	183	59.6	Reference					
	Mild	70	172	40.7	0.66	(0.48–0.93)		0.54	(0.38–0.77)	
	Moderate	196	492	39.9	0.64	(0.49–0.84)		0.49	(0.37–0.66)	
	Severe	346	1,170	29.6	0.48	(0.38–0.62)		0.38	(0.29–0.49)	
	Very severe	42	284	14.8	0.25	(0.17–0.36)	<0.001	0.21	(0.14–0.30)	<0.001

Appendix K *continued*		**Number live births**	**Time at risk (pys)**	**Rate (per 100 pys)**	**Unadjusted***			**Adjusted†**		
					SHR	**(95 CI%)**	**P-value**	**SHR**	**(95 CI%)**	**P-value**
Treatment variables										
Qualified for public funding	No	113	341	33.1	Reference					
	Yes	650	1,959	33.2	1.07	(0.88–1.31)	0.494			

* *All independent variables with an unadjusted p<0.20 were tested for inclusion in the adjusted model, but only those that improved the model fit (as assessed by a reduced AIC) remained in the model and were reported in the final model*

† *Simultaneously adjusted for all variables reported in the adjusted analysis*

APPENDIX L: AGE-STANDARDISED RATES OF INFERTILITY, PELVIC INFLAMMATORY DISEASE AND ECTOPIC PREGNANCY BY DISTRICT HEALTH BOARD IN WOMEN AGED 15–44 YEARS (AVERAGE FOR 2005–2009)

Infertility

DHB	Age-standardised rate of infertility per 100,000 women (95% CI)
Northland	65.4 (38.2–104.5)
Waitemata	68.3 (53.7–85.5)
Auckland	85.4 (68.5–105.3)
Counties Manukau	52.7 (39.3–69.2)
Waikato	33.2 (21.0–49.7)
Lakes	44.7 (20.4–85.0)
Bay of Plenty	89.6 (61.6–126.0)
Tairawhiti	39.3 (9.2–107.9)
Hawkes Bay	36.6 (17.8–66.6)
Taranaki	31.6 (12.0–67.3)
Mid Central	35.7 (18.1–63.1)
Whanganui	28.9 (6.4–81.3)
Capital and Coast	59.5 (42.5–81.2)
Hutt Valley	66.3 (40.2–102.9)
Wairarapa	42.6 (8.7–127.5)
Nelson Marlborough	175.6 (127.1–236.7)
West Coast	89.7 (29.4–208.1)
Canterbury	45.8 (33.5–61.0)
South Canterbury	147.7 (79.4–250.7)
Southern	85.3 (63.1–112.5)

Pelvic inflammatory disease

DHB	Age-standardised rate of PID per 100,000 women (95% CI)		
	All primary and secondary diagnoses	Primary diagnoses only	Confirmed diagnoses only
Northland	288.5 (226.2–362.4)	95.4 (61.7–140.8)	28.4 (11.6–57.6)
Waitemata	290.6 (259.3–324.7)	86.5 (69.7–106.1)	16.9 (10.1–26.6)
Auckland	301 (268.5–336.5)	76.5 (60.6–95.5)	17.9 (10.6–28.2)
Counties Manukau	426.6 (386.8–469.5)	130.2 (108.6–154.8)	33.5 (23.1–47.2)
Waikato	252.1 (216.5–291.9)	75.5 (56.8–98.5)	32.1 (20.3–48.3)
Lakes	322 (247.8–411.3)	122.8 (78.9–182.2)	33.6 (13.0–70.5)
Bay of Plenty	273 (221.5–332.9)	79.8 (53.1–115.1)	29.6 (14.6–53.4)
Tairawhiti	462.7 (330.2–630.4)	151.3 (80.8–258.0)	57.1 (18.5–133.5)
Hawke's Bay	273.6 (215.9–342.0)	90.8 (59.1–133.2)	29.9 (13.1–58.0)
Taranaki	201.4 (143.8–274.3)	56.7 (28.6–100.7)	23.7 (7.4–56.5)
Mid Central	255.1 (203.7–315.4)	74.7 (48.5–110.0)	36.3 (18.7–63.4)
Whanganui	340.8 (241.7–466.8)	136.5 (77.3–223.2)	19.7 (3.1–66.1)
Capital and Coast	193.6 (161.5–230.2)	58.3 (41.4–79.9)	18.3 (9.5–31.9)
Hutt Valley	232.9 (180.7–295.4)	82.4 (52.7–122.9)	26.2 (11.2–52.2)
Wairarapa	224.6 (125.0–372.4)	111.2 (45.2–227.2)	44.2 (8.7–132.0)
Nelson Marlborough	196.5 (144.4–261.2)	63.4 (35.4–104.7)	51.6 (26.6–90.1)
West Coast	277.5 (157.2–453.3)	92.4 (30.3–213.4)	33.9 (4.7–121.7)
Canterbury	287.2 (255.0–322.3)	82.7 (65.9–102.6)	32.7 (22.5–46.0)
South Canterbury	242.7 (151.6–368.1)	97.7 (44.0–187.1)	45.2 (12.6–114.6)
Southern	179.1 (147.1–216.0)	53.0 (36.5–74.4)	28.9 (16.9–46.0)

Ectopic pregnancy

DHB	Age-standardised rate of ectopic pregnancy per 100,000 women (95% CI)	Age-standardised rate of ectopic pregnancy per 1,000 live births (95%CI)
Northland	121.9 (82.9–172.6)	14.6 (9.9–20.7)
Waitemata	112.2 (93.1–134.1)	17.1 (14.1–20.5)
Auckland	93.2 (75.9–113.4)	16.8 (13.6–20.5)
Counties Manukau	120.1 (99.4–143.9)	14.8 (12.2–17.7)
Waikato	101.5 (79.4–128.0)	14.7 (11.4–18.6)
Lakes	145.9 (97.1–210.4)	17.6 (11.6–25.6)
Bay of Plenty	111 (79.1–151.5)	14.5 (10.3–19.7)
Tairawhiti	127.6 (63.1–228.9)	16.6 (8.0–30.1)
Hawkes Bay	125.3 (86.9–174.6)	16.3 (11.2–22.8)
Taranaki	100 (60.8–154.9)	14.1 (8.5–22.1)
Mid Central	73.5 (47.1–109.4)	10.7 (6.8–16.0)
Whanganui	109.6 (56.1–191.9)	13.6 (6.8–24.2)
Capital and Coast	71.5 (52.8–94.6)	12.9 (9.4–17.3)
Hutt Valley	109.5 (74.7–154.7)	16.3 (11.1–23.1)
Wairarapa	97.1 (35.0–211.3)	11.5 (4.2–25.1)
Nelson Marlborough	100.4 (63.4–150.7)	15.2 (9.7–22.9)
West Coast	137.8 (57.8–275.4)	20.2 (8.5–40.2)
Canterbury	106.9 (87.6–129.0)	17.9 (14.7–21.7)
South Canterbury	114.4 (54.4–210.5)	16.6 (7.9–31.3)
Southern	94.3 (71.3–122.4)	17.0 (12.8–22.0)

APPENDIX M: MULTIVARIATE POISSON REGRESSION MODELS FOR THE RISK OF HOSPITAL ADMISSION FOR INFERTILITY, PELVIC INFLAMMATORY DISEASE AND ECTOPIC PREGNANCY DURING 2005–2009

Infertility

	IRR	95% CI	P-value
Area			
Southern DHB	1.00	–	<0.001
Rest of South Island	0.90	(0.76–1.07)	
North Island	0.67	(0.58–0.79)	
Ethnic group and age group (years)			Interaction: p=0.023 (Wald test)
European and Other			
15–24	1.00	–	
25–29	6.34	(4.91–8.18)	
30–34	11.70	(9.21–14.86)	
35–39	11.03	(8.69–14.00)	
40–44	2.39	(1.81–3.15)	
Māori			
15–24	1.03	(0.68–1.56)	
25–29	0.82	(0.60–1.12)	
30–34	0.54	(0.41–0.73)	
35–39	0.49	(0.36–0.66)	
40–44	0.41	(0.22–0.75)	
Pacific			
15–24	0.63	(0.30–1.32)	
25–29	1.06	(0.71–1.57)	
30–34	1.01	(0.73–1.41)	
35–39	0.95	(0.67–1.34)	
40–44	1.08	(0.58–2.02)	
Asian			
15–24	0.85	(0.51–1.40)	
25–29	1.25	(0.94–1.67)	
30–34	1.48	(1.18–1.86)	
35–39	1.33	(1.05–1.68)	
40–44	1.40	(0.93–2.12)	

Infertility *continued*	**IRR**	**95% CI**	**P-value**
Deprivation decile			
Linear term	1.15	(0.17–1.25)	p=0.001
Quadratic term	0.99	(0.99–1.00)	p=0.033

Pseudo r^2 0.211 *Over dispersion (alpha) p<0.001*

PID: All primary and secondary diagnoses

	IRR	95% CI	P-value
Area			p<0.001
Southern DHB	1.00	–	
Rest of South Island	1.45	(1.30–1.62)	
North Island	1.41	(1.28–1.56)	
Ethnic group and age group (years)			Interaction: p<0.001
European and Other			(Wald test)
15–19	1.00	–	
20–24	1.23	(1.08–1.42)	
25–29	1.26	(1.09–1.44)	
30–34	1.19	(1.04–1.37)	
35–39	1.16	(1.01–1.32)	
40–44	0.75	(0.65–0.86)	
Māori			
15–19	1.77	(1.51–2.07)	
20–24	2.00	(1.71–2.33)	
25–29	1.34	(1.15–1.62)	
30–34	1.24	(1.04–1.48)	
35–39	1.06	(0.89–1.27)	
40–44	1.20	(0.98–1.47)	
Pacific			
15–19	1.39	(1.12–1.73)	
20–24	2.22	(1.84–2.70)	
25–29	1.96	(1.61–2.40)	
30–34	1.90	(1.66–2.32)	
35–39	2.08	(1.70–2.55)	
40–44	2.41	(1.92–3.03)	
Asian			
15–19	0.15	(0.10–0.23)	
20–24	0.33	(0.27–0.42)	
25–29	0.82	(0.68–1.00)	
30–34	1.18	(0.98–1.42)	
35–39	1.05	(0.87–1.27)	
40–44	1.15	(0.93–1.42)	
Deprivation decile			p<0.001
Linear term	1.09	(1.08–1.10)	

Pseudo r^2 0.161 *Over dispersion (alpha) p<0.001*

PID: Primary diagnoses only

	IRR	95% CI	P-value
Area			p<0.001
Southern DHB	1.00	–	
Rest of South Island	1.55	(1.29–1.86)	
North Island	1.53	(1.29–1.80)	
Ethnic group and age group (years)			Interaction: p<0.001
European and Other			(Wald test)
15–19	1.00	–	
20–24	0.98	(0.81–1.13)	
25–29	0.74	(0.62–0.88)	
30–34	0.50	(0.42–0.61)	
35–39	0.57	(0.48–0.68)	
40–44	0.47	(0.39–0.56)	
Māori			
15–19	1.45	(1.19–1.76)	
20–24	1.63	(1.32–2.01)	
25–29	1.36	(1.06–1.73)	
30–34	1.69	(1.31–2.18)	
35–39	1.45	(1.13–1.87)	
40–44	1.48	(1.12–1.94)	
Pacific			
15–19	0.84	(0.63–1.14)	
20–24	1.47	(1.12–1.93)	
25–29	1.49	(1.10–2.02)	
30–34	1.81	(1.31–2.51)	
35–39	1.95	(1.43–2.65)	
40–44	2.13	(1.53–2.98)	
Asian			
15–19	0.14	(0.08–0.25)	
20–24	0.25	(0.18–0.37)	
25–29	0.65	(0.47–0.90)	
30–34	1.00	(0.71–1.40)	
35–39	0.68	(0.47–0.98)	
40–44	1.08	(0.78–1.51)	
Deprivation decile			p<0.001
Linear term	1.12	(1.10–1.14)	

Pseudo r^2 0.145 Over dispersion (alpha) p=0.003

PID: Confirmed diagnoses only

	IRR	95% CI	P-value
Area			p<0.001
Southern DHB	1.00	–	
Rest of South Island	1.30	(1.02–1.66)	
North Island	0.82	(0.66–1.03)	
Ethnic group and age group (years)			Interaction: p<0.001
European and Other			(Wald test)
15–19	1.00	–	
20–24	1.34	(1.01–1.79)	
25–29	1.28	(0.96–1.71)	
30–34	1.67	(1.28–2.17)	
35–39	1.52	(1.17–1.98)	
40–44	1.17	(0.89–1.55)	
Māori			
15–19	1.50	(1.06–2.13)	
20–24	1.50	(1.07–2.09)	
25–29	1.41	(0.98–2.03)	
30–34	1.13	(0.81–1.57)	
35–39	1.24	(0.88–1.73)	
40–44	1.49	(1.04–2.14)	
Pacific			
15–19	0.50	(0.23–1.09)	
20–24	1.12	(0.67–1.87)	
25–29	1.39	(0.84–2.28)	
30–34	0.98	(0.59–1.62)	
35–39	1.77	(1.18–2.65)	
40–44	2.16	(1.38–3.36)	
Asian			
15–19	0.07	(0.01–0.49)	
20–24	0.16	(0.06–0.38)	
25–29	0.56	(0.31–1.02)	
30–34	0.59	(0.35–1.00)	
35–39	1.04	(0.68–1.59)	
40–44	1.08	(0.67–1.74)	
Deprivation decile			p<0.001
Liner term	1.11	(1.09–1.14)	

Pseudo r^2 0.163 *Over dispersion (alpha) p=0.298*

Ectopic pregnancy

	IRR	95% CI	P-val
Area			
Southern DHB	1.00	–	p<0.001
Rest of South Island	0.99	(0.86–1.14)	
North Island	0.85	(0.75–0.97)	
Ethnicity & age group (years)			Interaction: p<0.001
European			(Wald test)
15–19	1.00	–	
20–24	0.98	(0.81–1.20)	
25–29	0.78	(0.64–0.94)	
30–34	0.68	(0.57–0.82)	
35–39	0.88	(0.73–1.07)	
40–44	1.35	(1.07–1.71)	
Māori			
15–19	0.39	(0.29–0.51)	
20–24	0.69	(0.58–0.83)	
25–29	1.05	(0.89–1.25)	
30–34	1.27	(1.07–1.51)	
35–39	0.99	(0.80–1.23)	
40–44	0.60	(0.40–0.90)	
Pacific			
15–19	0.42	(0.26–0.67)	
20–24	0.54	(0.42–0.71)	
25–29	0.93	(0.75–1.16)	
30–34	1.34	(1.07–1.66)	
35–39	0.93	(0.71–1.22)	
40–44	0.67	(0.42–1.08)	
Asian			
15–19	0.98	(0.46–2.09)	
20–24	0.50	(0.36–0.71)	
25–29	0.85	(0.68–1.06)	
30–34	1.02	(0.83–1.25)	
35–39	1.25	(0.99–1.57)	
40–44	1.42	(0.98–2.07)	
Deprivation decile			p<0.001
Linear term	1.06	(1.04–1.07)	

Pseudo r^2 0.071 *Over dispersion (alpha) p=0.034*